Metal-Free C_{sp2}-H Borylation using Borenium cations

Master's thesis

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Abstract

C-H bonds are abundantly present in organic compounds and therefore represent large class of targets for activation in modern synthetic chemistry. Starting from simple and usually inexpensive compounds, direct activation of C-H bonds provides atom efficient (low waste generation) access to highly functionalized products with high added value. One of the most desirable subclass of C-H bond functionalization is its transformation to C-B bond (borylation), as organoboron compounds are important and widely used building blocks in organic synthesis, in particularly pharmaceuticals, agricultural chemicals and organic materials. Traditionally, transition metal-based catalysts have been used for C-H borylation. Recently, interest has grown towards metal-free approaches. This thesis is focused on the development of metal-free C_{sp2}-H borylation of arenes by coupling two main concepts: borenium cations and Frustrated Lewis Pairs (FLPs).

Borenium cations are positively charged boron species possessing two σ-bound substituents, and the third coordination site occupied by a ligand (L) bound through coordinative dative interaction. Due to relative stability ensured by donor ligand and enhanced reactivity owing to unsaturated coordinate sphere and positive charge, chemistry of boreniums attracted considerable attention.

FLPs comprise separated (intermolecular) or bound within one molecule (intramolecular) Lewis acidic and Lewis basic components, which are prevented from formation of classical Lewis adduct due to steric repulsion. Since FLPs posses unquenched reactivity they are capable to cleave heterotically σ and π chemical bonds, including C-H bonds.

The method showed in the present work implies cooperative actions of 2-aminopyridinyl-borenium based FLPs, comprising borenium cation as LA component, and bulky aminopyridine ligand as LB component to borylate aromatic C_{sp2}-H bonds. In this approach, LA serves as a reagent itself (source of boron), while LB (ligand), which abstract proton upon C-H bond cleavage, can be fully recovered from the reaction mixture. Thus, this approach offers high atom efficiency and low waste generation. We achieved borylation of electron-rich thiophenes, furans, and pyrroles under ambient conditions. Further we dedicated our efforts to improve efficiency and economical aspect of the proposed method.

Contents

List of abbreviations and symbols

TM – transition metal

FLP – Frustrated Lewis Pairs

LB – Lewis base

LA – Lewis acid

L – Ligand

Ar – aryl

2-AAB – *ansa*-aminoborane

d^{t}bpy – 4,4′-Di-*tert*-butyl-2,2′-dipyridyl

COD – cyclooctadiene

Me – methyl

pin – pinacol

Cat – catecholato

ppm – parts per million

BCF – tris(pentafluorophenyl borane)

DCM – CH_2Cl_2

TMP – 2,2,6,6-tetramethylpiperdine

DIPEA – N,N-Diisopropylethylamine

Ar – aryl

TLC – thin layer chromatography

TLC/MS – thin-layer chromatography/mass spectrometry analysis

Et – ethyl group

$CbBr_6$ – [*closo*-1-H-$CB_{11}H_5Br_6$]$^-$

Cp’ – C_5H_5

Piv – pivaloyl

Ts – tosyl

Pip – piperidine

$PtBu_3$ – Tri-tert-butylphosphine

Introduction

Development of highly efficient and sustainable synthetic methods secure progress in accessing complex organic molecules and functional materials. Among those methods direct C-H bond functionalization is highly attractive strategy from the viewpoints of pharmaceutical and chemical industries, providing efficient and sustainable way to convert highly abundant chemicals into functionalized high added value products. Transformation of C-H bond to C-B bond, namely borylation, is among the most desired and widely used subclass of functionalization of C-H bond. Organoboron compounds, such as boronic esters have rich applications in organic synthesis including C-C cross-couplings, reduction, synthesis of alcohols, phenols and some other reactions. First appeared as early as 1900s[1], interest in preparation of organoboron compounds has been busted by the discovery of cross-coupling, which rendered these compounds widely used building blocks for more complex and valuable products.[2]

Traditional synthesis of organoboron compounds requires usage of stoichiometric amounts of organometallic reagents and/or transition metal (TM)--catalysts. In line with general concept of direct C-H functionalization, there is a particular interest in direct borylation of readily available arene and heteroarenes.[3] Since, aromatic C-H bonds can be cleaved by TMs because TMs can easily meditate two-electron transfer in catalytic processes, direct activating of C-H bond is dominated by TM catalysis often involving iridium[4]-, platinum[5]-, rhodium[6]- based catalysts. However, due to high toxicity, low abundance of TMs in the crust of Earth, and associated economic issues, there is growing interest to alternative metal-free activation modes, which, for instance, can be offered by Frustrated Lewis Pairs (FLPs), combinations of sterically separated Lewis Bases (LB) and Lewis acids (LA). Unlike TM catalysis when chemical transformations occur at the single metal center, FLPs induce σ and π bonds heterolytic splitting by cooperative action of the Lewis acid and base[7]. This provides means for heterolysis and activation of a number of challenging molecules, such as H_2, originally demonstrated in 2006[8]. More recently this concept has been extended towards cleavage of C-H bonds as well, and particularly more challenging C_{sp2}-H bonds of arenes and alkenes.

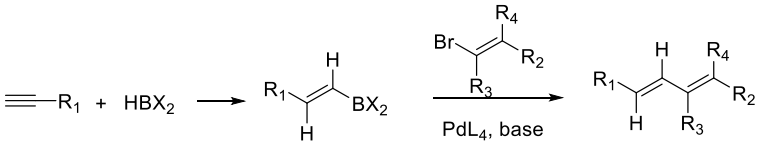
Literature review

Organoboron reagents

Organoboron compounds are extensively explored reagents in organic synthesis and catalysis and have wide applications in pharmaceutical and agrochemical area. Classic reactions include hydroboration and Suzuki-Miyarua cross-coupling reactions[60]. Traditionally, aryl boronate esters are often synthesized from arenes via multiple steps. These steps involve the presence of haloarene intermediates, either organometallic reagents in stoichiometric amount or cross-coupling reactions which is metal-catalyzed (e.g. Cu, Ni, Co, or Pd).[9] Recently, direct borylation of arene with sterically hindered iridium catalysts[10] was reported. While this method also have many limitations including steric, regioselectivity and economical aspects[11]. And borylation using FLP catalysts is becoming more and more popular right now and scientists are more interested in researching this method.

Boron reagents with vacant p-orbital can receive electrons, therefore they are used as Lewis acids due to the reason that they possess strong electrophilic property. The acidity can be controlled by adjusting electron and steric properties of substituents at boron.

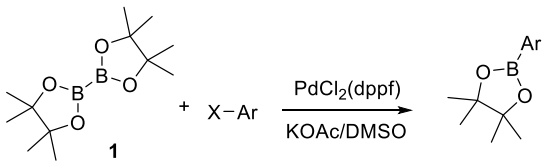
In 1860, Frankland for the first time prepared and isolated boronic acid, opening first chapter in organoboron chemistry.[12] In 1979, Miyaura N, Yamada K, and Suzuki A found a novel cross-coupling: tetrakis(triphenylphosphine)palladium in presence of base catalyzes reaction between 1-alkenylboranes synthesized via hydroboration of alkynes and 1-alkenyl halides to form conjugated dienes with high regio- and stereo-specificity in high yields (Scheme 1).[13]



Scheme 1 cross-coupling reaction

Pinacol esters of boronic acids RBpin received special attention as versatile reagents for cross-coupling reactions. In 1995, Ishiyama et al.[14] reported that aryl halides were borylated with bis(pinacolato)diboron (Scheme 2) catalyzed by Pd, representing the first one-step procedure for preparing arylboronic ester from aryl halides, which

enabled the facile synthesis of ArBpin units without transmetalation with stoichiometric organometallic reagents.



Scheme 2 Pd-catalyzed borylation of aryl halides

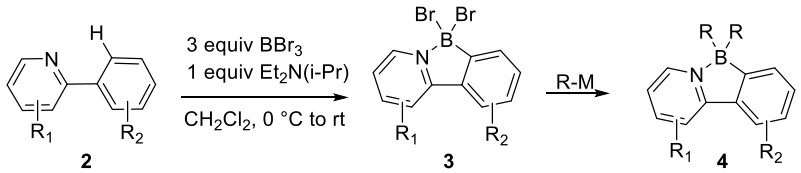
As a result of further developments of this methodology a range of complexes, comprising inexpensive, abundant and less toxic TM complexes, including Cu, Ni, Zn and Fe were reported[15].

Nobel metal catalysts

Direct borylation of arenes using nobel metal catalysts was an important approach towards organoboron compounds. Among them, Ir-based catalysts were extensively explored. For instance, direct arenes borylation by B_2pin_2 using $[Ir(X)(COD)]_2/d^tbpy$ (X= OMe or Cl) as catalyst was reported, and $16e^-$ intermediate $[Ir(d^tbpy)(Bpin)_3]$ was examined to be actual catalytically active substance during the process.[16]

Metal-free catalyst

In 2010, Murakami et al.[17] reported a borylation reaction of 2-arylpyridines with BBr_3 which was N-directed C-H bond borylation. The intermediate 2-(2-dibromoborylaryl)pyridine could be converted further to pyridine-borane complexes (Scheme 3).



Scheme 3 Metal-free direct C-H bond borylation

Borenium cations

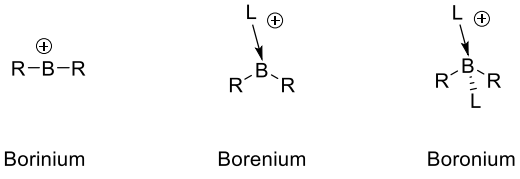
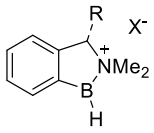


Fig 1 Borinium cations (I): two-coordinate by two substituents; borenium cations (II): three-coordinate; boronium cations (III) : four-coordinate

Positively charged boron species can be divided into three subclasses, depending on coordination number of boron (Fig 1). The boriniums bearing two-coordinate boron are the most reactive but not stable. Boroniums bearing four-coordinate boron are of high structural stability, but poorly reactive due to coordinative saturation. Boreniums possess two σ-bound substituents (R), one dative interaction with a ligand (L) which hold a third coordination position reducing the electron deficiency of boron and stabilizing the species. Due to relative stability ensured by donor ligand and enhanced reactivity owing to unsaturated coordinate sphere and positive charge, chemistry of boreniums attracted considerable attention[18].

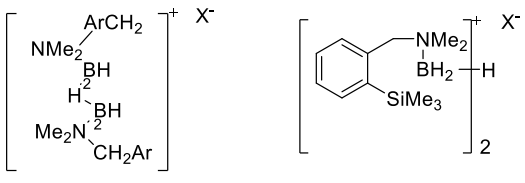
In Edwin Vedejs's study,[19] he synthesized borenium ions which are exceptionally potent electrophiles (Scheme 4). The electron deficiency in boron center was compensated by the electron pairs on nitrogen, while the stability of borenium ions have the requirement that the additional sources of electron density are present. In **5**, the necessary stabilization is achieved by the hindered pyridine derivatives bond to boron through the electron pair in nitrogen, and it is apparently achieved by a π-delocalization effect.



5

Scheme 4 Edwin Vedejs's compound

In Timothy S. De Vries's research,[20] during borylation, the participation of borenium species of hydron-bridged cations increase the promising possibility of C-H insertion mechanisms (Scheme 5).



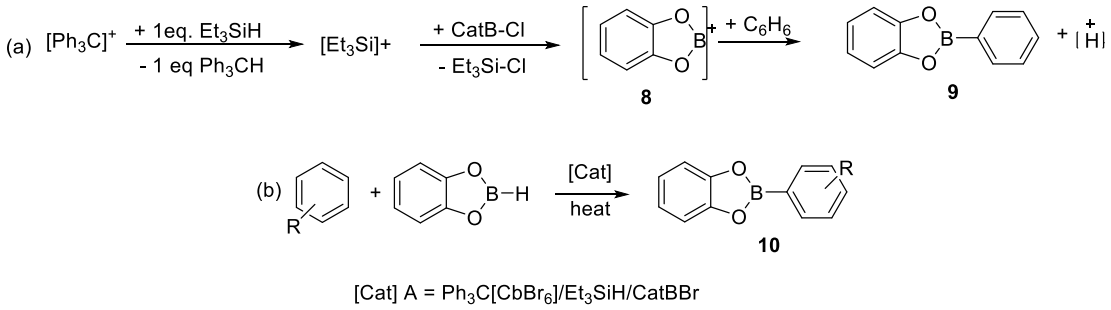
6 **7**

Scheme 5 Timothy S. De Vries's reserach

Metal free $C_{sp1, sp2, sp3}$-H borylations

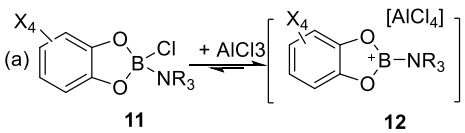
In the recent decade, the development of main group chemistry and especially FLP chemistry offered some alternative metal-free activation modes for C-H bonds. Terminal acetylenes are easy to have C_{sp}-H splitting because they are acidic and they have highly sterically available C-H bond. On contrary, there are only few examples indicating the reactivity for C_{sp2}-H and C_{sp3}-H borylation in FLP chemistry.

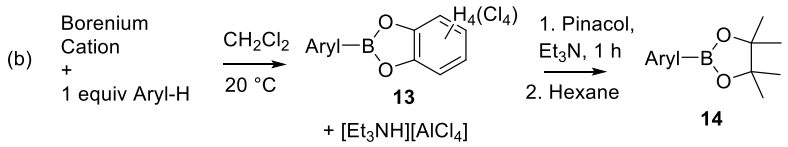
In 2010, Ingleson and his team reported[21] that boron cations with chelate constraint are highly electrophilic to produce borylated arenes. He demonstrated that borinium cations with linear and chelate restrained are two kinds boron stabilization degrees according to π-donation. Chelated restrained boron cations are one of the strongest Lewis acids for the reason that its electrophilicity is increased by the nonlinear geometry at boron, it also have a sterically more obtainable boron cation. In his research, catalytic quantities of $[Et_3Si][CbBr_6]$ and CatBX [Cat=catecholato, $C_6H_4O_2^{2-}$, X= Cl or Br] can produce borylation arenes in high-yielding under low temperature (Scheme 6), and H_2 is the only byproduct in this atom economy cycle.



Scheme 6 (a) Arene borylation by chelate restrained boron cations. (b) Superacid-Catalyzed aromatic borylation

Later, his team reported new Lewis acids: catecholato-ligated borenium cations which are electrophilic enough to borylate various arenes: thiophenes, anilines and N-heterocycles. The reaction mechanism resembles Friedal-Crafts chemistry.[22] The borenium cation is formed by halide abstraction with $AlCl_3$ (Scheme 7). $AlCl_3$ is strong electrophile which is a key prerequisite for electrophilic aromatic substitution. The CatBCl(**11**) does not react with $AlCl_3$ as such, but the reaction occurs fast when $AlCl_3$ is added to amine adduct of **11**.

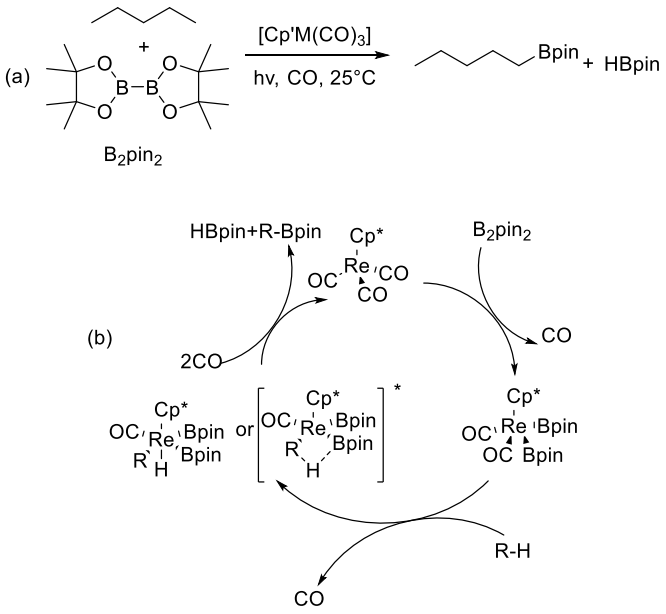




Scheme 7 (a) borenium cations formed during halide abstraction with $AlCl_3$. (b) direct borylation of arenes using borenium cations.

C_{sp3}-H borylation

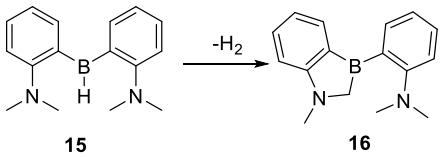
Chen et al. reported a rhenium-catalyzed process that produce organoboranes from alkanes (Scheme 8) which are common and valuable synthetic building blocks.[23] In the reaction, TM-boryl complexes (L_nM-BR_2, where L is a ligand, M is a metal, and R is an organic substituents) are employed. Higher reactivity of primary over secondary C-H bonds has been observed in stoichiometric oxidative addition and σ-bond metatheses. Later, the same group reported to catalytic borylation of alkanes. [24] In this report, linear alkylboranes can be obtained from commercially available boron reagents using rhodium complex CpRh(η^4-C_6Me_5) as a catalyst under thermal conditions. This kind of alkane functionalization can transfer a functional group to the end of an alkyl chain offering a tool for late stage functionalization of more complex structures.



Scheme 8 (a) Stoichiometric reaction of B_2pin_2, Cp' = C_5H_5, C_5H_4Me, C_5Me_5; M=Mn, Re. (b) Proposed mechanism

Fontaine and co-worker[25] reported that *ansa*-aminoboranes are able to conduct C_{sp3}-H bonds cleavage by using classical metal-free ambiphilic activation, resulting in

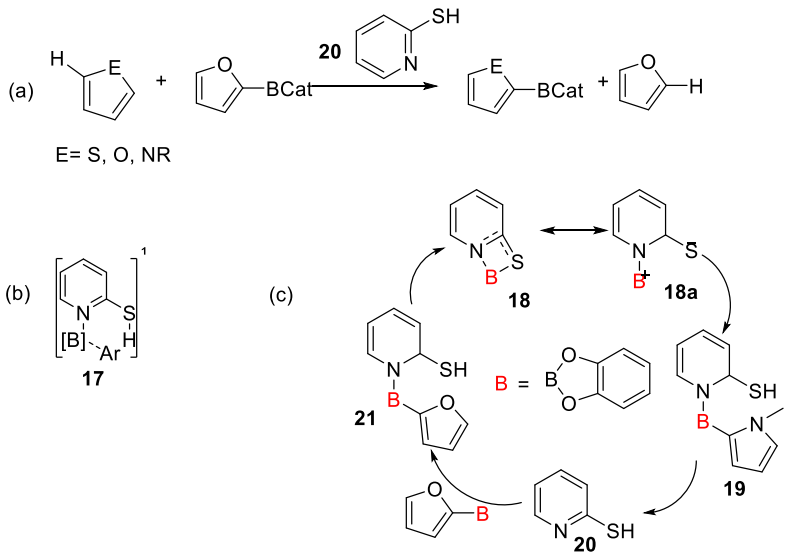
abnormal boron-containing heterocycles (Scheme 9). Corresponding DFT studies of activation ability of B/N Lewis pair were carried out to locate a transition state can generate ammonium borohydride zwitterion. Under mild heating, the C-H bond of the methyl group which is in nitrogen α position is activated by $(2\text{-}NMe_2\text{-}C_6H_4)_2BH$, a ambiphilic molecule to produce an unprecedented N-B heterocycle.



Scheme 9 C_{sp3}-H activation

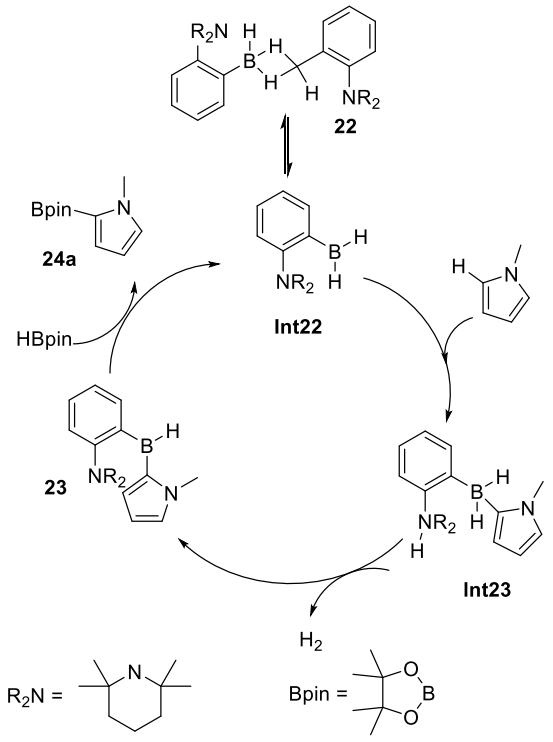
C_{sp2}-H borylation

Rochette et al.[26] reported an elegant protocol for borylation of heterocycles using ambiphilic aminoboranes molecules as catalyst (Scheme 10). The transfer borylation of heteroarenes is mediated by metal-free catalyst 2-mercaptopyridine. In this process, arylboronates are used as borylation agents. This is so-called isodesmic C-H functionalization transformation. Along with high reaction yields, this transformation features outstanding tolerance to many functional groups. The six-membered transition state **17** is a key element because the efficient activation of C-H bonds using Lewis frustrated pairs preferably connected through an aromatic system to facilitate electronic interaction. Substrate scope comprised various N-alkylated indoles substituted by electron-withdrawing and electron-donating groups on pyrroles and electron-rich thiophenes. The reaction energy profile was analyzed by DFT calculations. In the calculated structure of **18**, the bond length between boron and sulfur atom was found 2.1 A. Because the bond is weak, **18a** can be easily formed with the nucleophilic character in the thioamide and borenium character in the boron center, and therefore capable for FLP-like C-H activation.

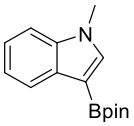


Scheme 10 (a) Transition state; (b) Metal-Free Transfer C-H Borylation; (c) Proposed catalytic cycle

Fontaine and his team[27] reported a FLP catalyzed metal-free C-H borylation of heteroarenes, previously reported by our group[28]: *ansa*-aminoborane, with BH_2 as the smallest possible Lewis acidic center and bulky TMP group as Lewis basic center. Thiophene can be easily borylated in room temperature. indicating, that such 2-AABs are powerful FLPs. In this process, presumably concerted C-H bond cleavage happens via proton abstraction by Lewis basic amino group and simultaneous C_{sp2}-H bond electron density transfer to a Lewis acidic borane (Scheme 11). The bulky amine center favors proton abstraction, while preventing possible head-to-tail dimerization of catalyst. This borylation protocol was proved to be tolerant towards various kinds of functional groups including hexamethylphosphoramide, epoxides, halides, less basic amines, and ethers. By conducting the reaction with electron-withdrawing *tert*-butyloxycarbonyl group(BOC), the critical elements for the reaction to proceed are electronic parameters. The borylation reaction with 1-methylindole preferred 3 position which is electron rich rather than 2 position with the conversion over 99% (Scheme 12).



Scheme 11 Proposed mechanism of 1-methylpyrrole borylation with catalyst **22**



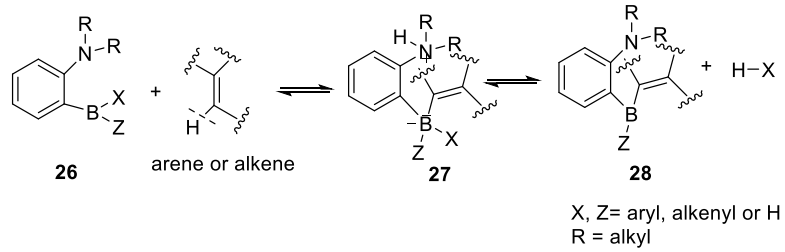
25
Conv: >99%
Yield: 85%

Scheme 12 product from borylation of 1-methylindole

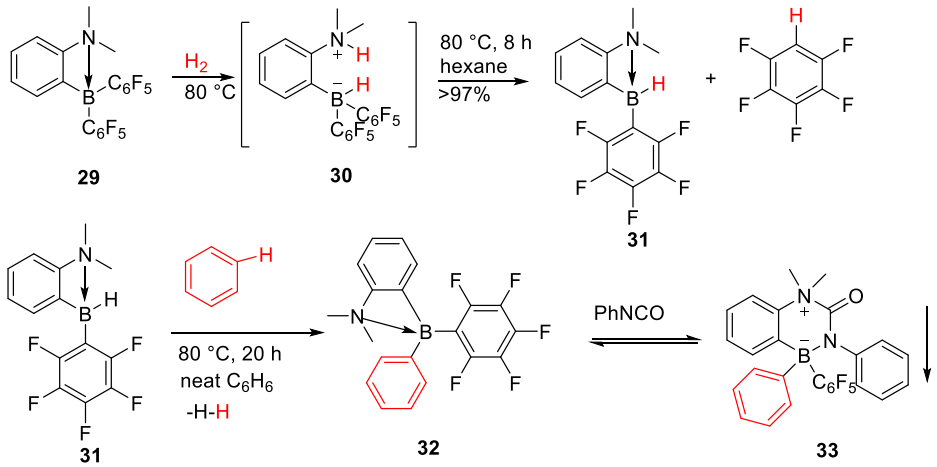
In this report, borylation proceeds rapidly for electron-rich thiophene, again it shows that the critical elements for the occurrence of catalysis are electron-rich substrates. Density functional theory (DFT) calculations were carried out to clarify the reaction mechanism applying 1-methylpyrrole as a model substrate. In the proposed mechanism (Scheme 11), the dimer of the catalyst **22** first dissociate to form **Int22**, then during the C-H activation to form zwitterionic species **Int23**. Then the calculation predicts the rapid release of H_2 to form **23**. **24a** was formed in the presence of HBpin. Then via a four-center sigma-bond metathesis, **22** was regenerated in the process. The overall kinetic isotope effect (KIE) is 1.8. This KIE is relatively low and is close to that observed synergistic metalation deprotonation of palladium-catalyzed arylation reaction with the similar substrates (KIE=2.1, at 100℃).

Alongside Repo et al.[29] reported the 2-*ansa*-aminoboranes insertion into C_{sp2}-H bonds

of arenes, hetarenes, and alkenes (**26**, Scheme 13) as a common reactivity pattern. This work rooted in early research which reported hydrogenation of internal alkynes with H_2 catalyzed by **31** (Scheme 14), which could be in situ generated from precatalyst **29**.[30] While **29** reacts with H_2 reversibly at room temperature to produce adduct **30,** under elevated temperature, **31** and pentafluorobenzene are formed from the intramolecular protonolysis of the B-C_6F_5 bond. During this study it was noted, that preparation of **31** in aromatic solvents, for instance C_6H_6, gives substantially lower yields then in hexane, leading to the discovery that **31** actually reacts with arenes. DFT analysis between **31** and C_6H_6 indicated a two- step mechanism in this reaction, involving splitting of C-H bond (concurrent with B-C bond formation), followed by subsequent H_2 elimination. The activation of C-H bond featured high activation energy barrier consistent with rasied temperatures essential for the reaction. Borylation is predicted to be endergonic but both kinetically and thermodynamically accessible. Accordingly operating the reaction in a closed system is unfavored; however, constant liberation of the gaseous H_2 and a large amount of excess substrates from the solution phase obviously shifts the balance towards the borylation product.

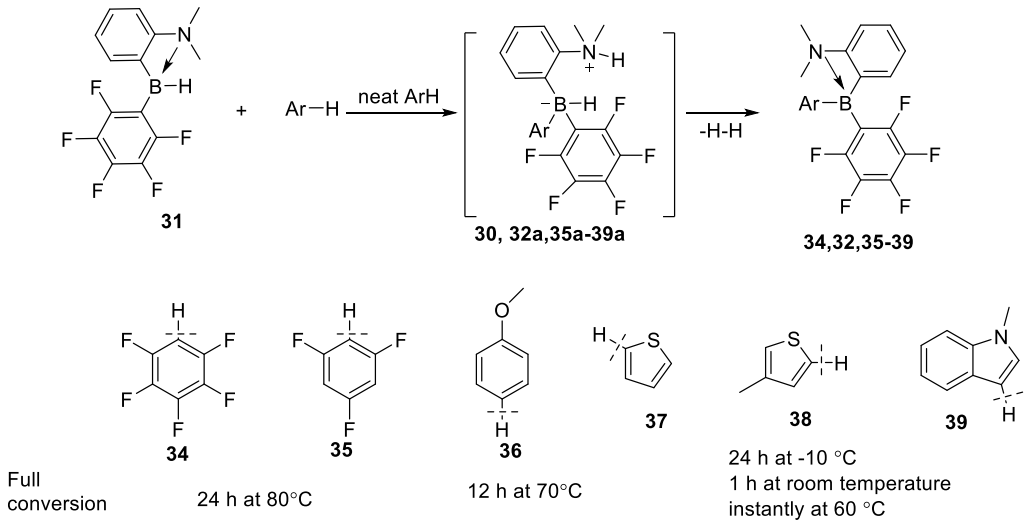


Scheme 13 React pattern of dehydroborylation of arenes



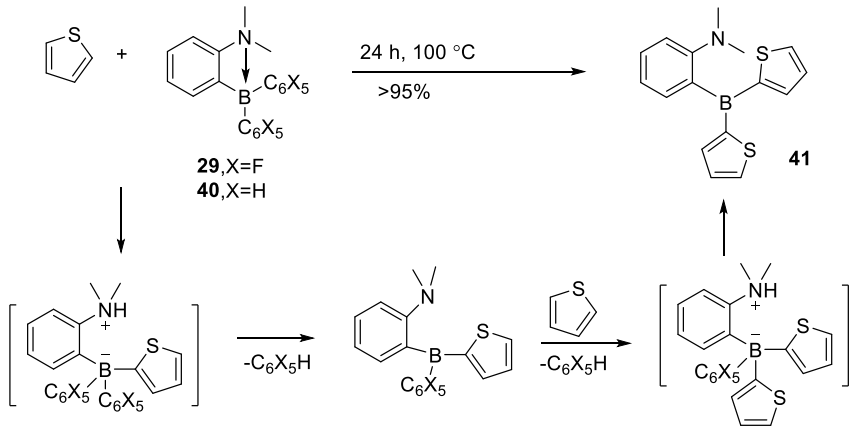
Scheme 14 Formation of the active catalyst species.

Many different substrates were tried with this 2-AABs reactivity pattern (Scheme 15), they all have better and faster conversion under higher temperature.



Scheme 15 C-H Boryaltion of Arenes with **31**

31 was used in theses reactions as it is the most reactive species. ^{11}B NMR analysis suggested, that these 2-AABs (**34**, **32**, **35-39**) exist as intramolecular N-B adducts, and boron signal appears in the range 8-20 ppm. The change in value proves the connection between the electron -accepting or -donating characteristics of the aryl substituents and the strength of N-B bond. Alternative approaches to the dehydrogenative pathway revealed the reactivities of 2-AABs' C-H. The sp^2 substituents including $-C_6F_5$ and $-C_6H_5$ groups can easily go through the protonative cleavage of B-C bond, making it possible to exchange aryl groups (Scheme 16).

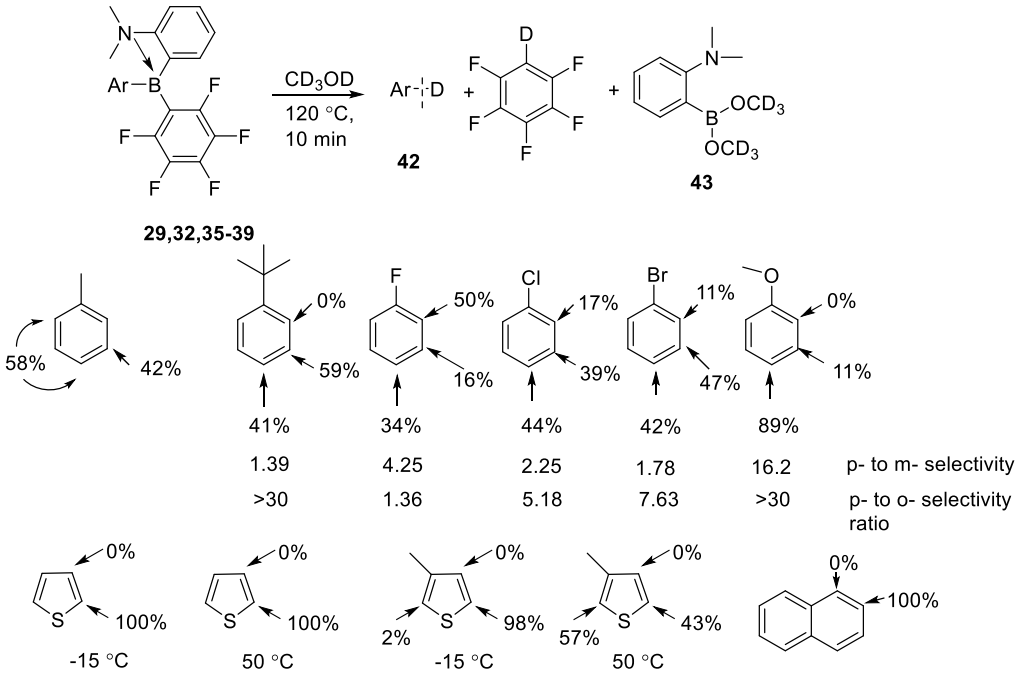


Scheme 16 C-H borylation of thiophene with interchange of Aryl groups

Since olefins is the major target for C_{sp2}-H functionalization, the exchange of aryl groups with alkenyls was also attempted. And the result revealed that the borylation

product is not single and alkenes trans-selective C-H borylation is the exclusively product. Mechanistic study based on NMR and X-ray crystal structures analysis confirmed assumption of α-C-H insertion to form zwitterionic FLP adduct. Thus, the study revealed that C_{sp2}-H borylation and intramolecular C_{sp2}-B protonation is a general reactivity mold inherent to the frustrated 2-AAB core.

The regioselectivity of borylation was checked by mixing the product mixtures with CD_3OD. The deuteration decomposition of the C_{sp2}-B bond can selectively label the carbon in arene by deuterium, because this is the reverse step to C-H insertion procedure. The *para*- over *ortho*-borylation preference for bromobenzene, chloro-, and fluoro- has been increasing, and the ortho borylation of anisole and tert-butylbenzene has been completely suppressed, which indicates the significant steric effect influences (Scheme 17).

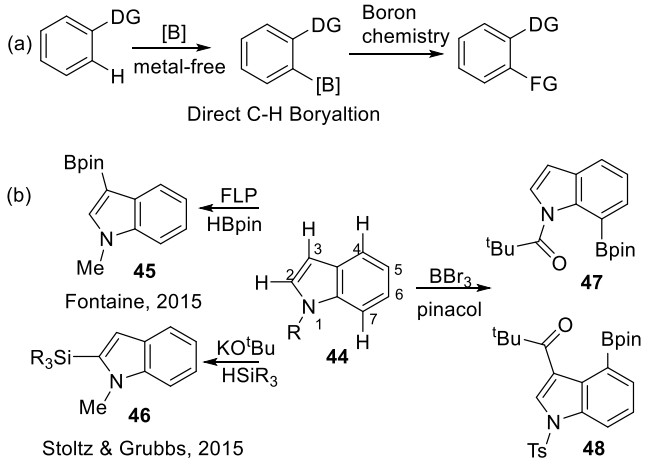


Scheme 17 Regioselectivity of borylation

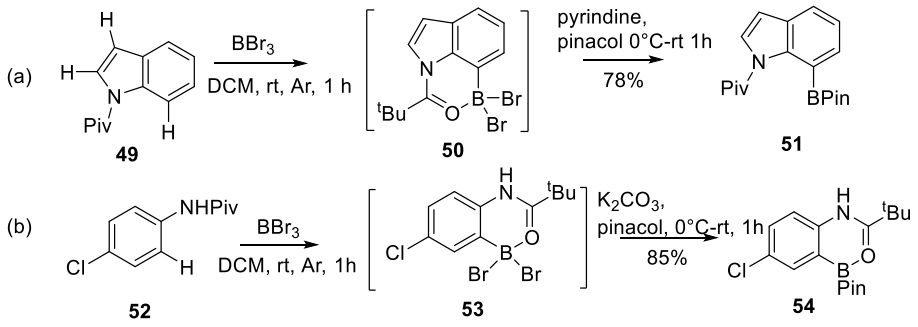
The observed regioselectivity indicates that the borylation of arene is between classical aromatic electrophilic substitution mechanism and random product distribution. And it also reflected that the electrophilic properties of the attacking boron species matters, and together the proton is removed by the amino group. It was observed that the naphthalene exclusive β-borylation product was due to the combined effect from electronic and steric factor. Interestingly, self-borylation of **31** was observed by

deuteration experiments on the phenylene bridge connecting N and B centers. In **Fig. 2 69** is isoelectronic and isostructural to 2-AABs, which may possesses similar C-H borylating ability. The substituted 2-dimethylaminopyridinium salt is solid, air-stable and moisture-insensitive and it is used as a catalyst which catecholborane can borylate *N*-methylindole and 3-methylthiophene.

In 2019, Jiahong et al.[31] and coworkers reported a metal-free, direct activation and borylation of C-H bond by using BBr_3 as reagent and catalyst. C7 and C4-borylated indoles are produced by this gentle method and have broad functional group compatibility (Scheme 18). The reaction of N-pivaloyl indole with BBr_3 is conducted using dry DCM as solvent for one hour at room temperature without any additive and dibromoborane product is generated and confirmed by X-ray analysis. The pyridine was used as a base in the reaction with pinacol to get indole C7 product isolated in 78% yield. Then the C4-borylated indoles are examined and the treatment of the indole bearing an N-Ts group in the system provided the desired C4-borylated products (Scheme 19) with isolated yield of 88%. Various substituents were tolerated, including alkenyl, F, Cl, Br, I, phenyl, methyl and methoxy. The reaction conditions are compatible with heterocyclic motifs such as thiophene. There is obvious limitation that it has to be Piv group in the indole to form intermediates, which in not quite suitable for common arenes. But this method is quite alright and efficient for the specific indoles which can have wide application.



Scheme 18 (a) Metal-free, directed C-H borylation; (b)Metal-free site-selective C-H functionalization of indoles. DG, directing group; FG, functional group;

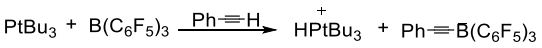


Scheme 19 (a) C7 position directed C-H borylation of indoles; (b) Directed C-H borylation of (hetero)arenes

C_{sp}-H borylation

Many recent examples proved that main-group reagents like borocations can help generate borylated alkenes in a metal-free manner. These kind of products are very useful in building more complex chemicals, often using cross-coupling reaction with organoborons.[32]

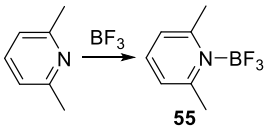
In 2009, Stephan and his group[33] reported a C_{sp}-H activation using phosphine/LA combination (Scheme 20). In this study, there are two reaction pathways that phosphine-alane hindered frustrated Lewis pairs or discrete phosphine-borane can react with phenylacetylene. Deprotonation provides a convenient facile pathway to alkynylborates, and the addition route provides specific zwitterionic olefinic phosphonium borates.



Scheme 20 C_{sp}-H activation

Frustrated Lewis pair

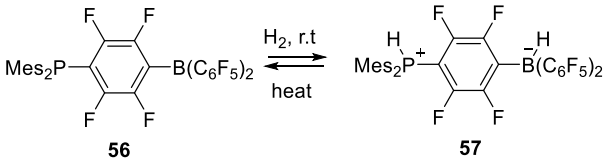
In 1923[34], Lewis acids is defined by Gilbert N. Lewis as electron-pair-acceptor and Lewis bases is defined as electron-pair-donor, which when combined together form Lewis adduct with strong dative bond. For instance, Brown et al.[35] reported that classical Lewis adduct was formed when the interaction of pyridine with simple boranes is examined, a stable adduct is formed by mixing lutidine with BF_3 (Scheme 21). Later, such adducts found wide application in organometallic chemistry, due to specific steric and electronic properties and the stereochemistry of ligands.



Scheme 21 Treatment of lutidine with BF_3

When sterically hindered, Lewis acid/base partners cannot form such adduct or form weak adduct and are called Frustrated Lewis pairs (FLPs). FLPs were found to be efficient in activating of small molecules through heterolytic cleavage of σ- or π- bonds to obtain the respective ionic or zwitterionic [Lewis acid]$^-$ -substrate- [Lewis base]$^+$ adduct. $RB(C_6F_5)_2$ is very strong electrophilic component, when it combined with bulky phosphines or amines, the Inter- or intramolecular combinations are formed and they are typical examples of frustrated Lewis pairs. Noteworthy, even Lewis adducts exhibiting no frustration (in other words classical Lewis adduct with dative bond) might form so-called thermally induced FLPs[36] which posses classical FLP reactivity.

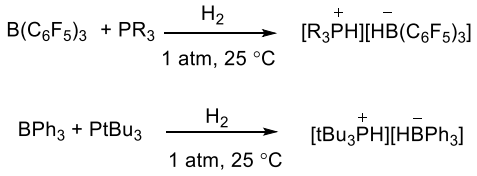
FLPs are proved be able to activate a large amount of unreactive substrates and they possess catalytic function in several transformation. In 2006 Stephan et al.[37] reported a compound $(C_6H_2Me_3)_2PH(C_6F_4)BH(C_6F_5)_2$ that reversibly cleave hydrogen (H_2) (Scheme 22). The highly Lewis acidic $B(C_6F_5)_3$ which has been already commonly used as polymerization cocatalyst was found to react with sterically demanding phosphine to form the product **56**. This intramolecular phosphinoborane reacts with H_2 at room temperatures and reform the starting material upon heating. These species were air and moisture stable and robust as such. The conversion was confirmed by X-ray analysis of generated adduct **57**. This discovery indicates a major progress in FLP chemistry.



Scheme 22 heterolytic cleavage of H_2

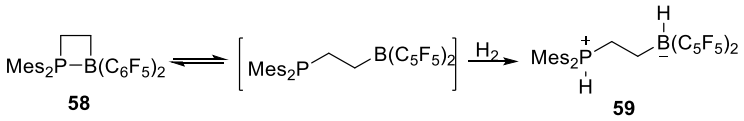
Later Stephan et al.[38] reported heterolytic cleavage of H_2 by separated phosphine and borane. Lewis acid-base adduct is formed during the reaction allowing consecutive reaction of the Lewis acidic and Lewis basic centers with H_2 (Scheme 23) to form zwitterionic adduct. FLPs reactivity can be modulated by the modification of acidity and basicity, steric properties of FLP components to favor or preclude the reaction with

H_2 under different reaction condition. For instance, when less acidic borane such as BPh_3 is used, cumulative strengths of FLP can be achieved by utilization of stronger base such as $PtBu_3$ to ensure reactivity towards hydrogen.



Scheme 23 Heterolytic Cleavage of H_2 by phosphine and borane

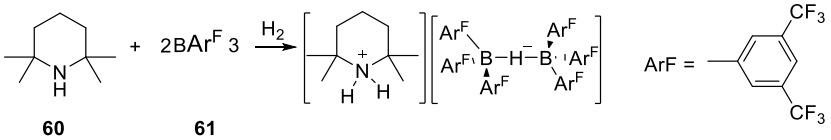
Around the same time, Erker, Stephan and their coworkers[39] discovered first cyclic intramolecular phosphane-borane adduct which can conduct rapidly dihydrogen activation to produce ethylene-bridged zwitterionic phosphonium-hydridoborate system (Scheme 24).



Scheme 24 the dihydrogen from a four-membered cyclic intramolecular phosphane-borane adduct

Since 2006, the development in FLP chemistry grow fast. In 2007[40], Stephan and his coworkers discovered that the reactivity of FLPs is depending on Lewis acidity. In their research, classical Lewis acid-base adducts $[LCPh_3][B(C_6F_5)_4]$ were synthesized following conventional chemistry, prompting nucleophilic aromatic substitution by the phosphine.

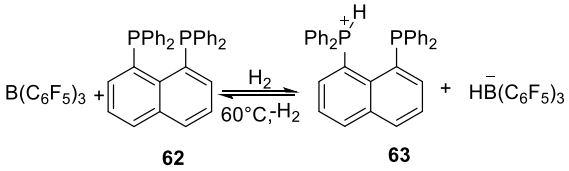
Typically, electron-withdrawing substituents with a hindered amine will promote Lewis acidity. In 2012, Thomas J. Herrington and his coworkers[41] found that is more powerful than $B(C_6F_5)_3$. It can form FLP with 2,2,6,6-tetramethylpiperidine which can cleave H_2. In his research, the acidity of **61** is measured by Gutmann-Beckett measurements. It is the first time that bridging borohydride is resulting from FLP-mediated H_2 heterolysis (Scheme 25) and the structure has been crystallographically characterized.



Scheme 25. H_2 activation by TMP and $BArF_3$

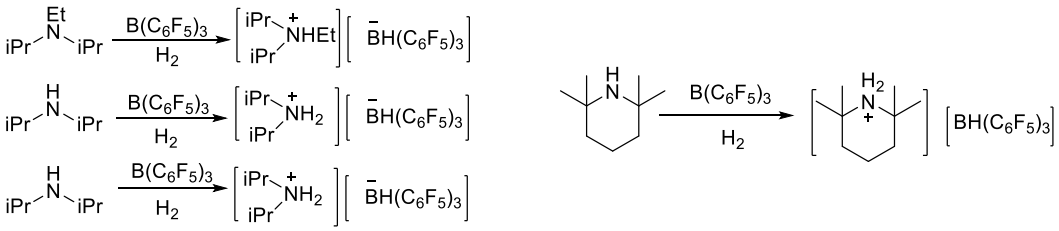
FLPs are also able to react with other small molecules. Zwitterionic species [tBu$_3$P(C$_2$H$_4$)B(C$_6$F$_5$)$_3$] can be generated by adding olefins to the combination of tBu$_3$P and B(C$_6$F$_5$)$_3$[42].

Erker et al.[43] developed an interesting new FLP, when combined with B(C$_6$F$_5$)$_3$, this diphosphine has been shown to activate H$_2$. The FLP can be regenerated at higher temperature for the resulting phosphonium borate losing H$_2$ (Scheme 26). Later on, this research group[44] also discovered that an amine functional group attached to the Cp ring of a forth group of curved metallocence scaffold can also be utilized as a proper base in a frustrated amine/B(C$_6$F$_5$)$_3$ Lewis pair. Adding one more B(C$_6$F$_5$)$_3$ to the doubly aminomethyl-substituted zirconocene substrate can generate a FLP, which can react with H$_2$ under mild condition.



Scheme 26 Synthesis and reactivity of alkyl-linked phosphino-boranes.

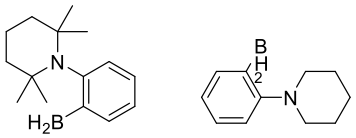
The research group of Repo and Rieger[45] reported an amine-borane system in 2008 and the system is derived from tetramethylpiperidine. This kind of system exhibits reversible H$_2$ activation. Reaction of iPr$_2$NEt and iPr$_2$NH with B(C$_6$F$_5$)$_3$ result corresponding ammonium salts, nonetheless, formation of ammonium-borate products (Scheme 27) was found when exposing the mixtures of iPr$_2$NH and B(C$_6$F$_5$)$_3$ to H$_2$. However, no reaction happens when employing BPh$_3$ instead of B(C$_6$F$_5$)$_3$ indicating the speculation of CF-HN interaction play a part in bringing amine close enough to borane in order to permit cooperative activation of H$_2$, and also the difference in Lewis acidity.



Scheme 27 H$_2$ activation by amines and B(C$_6$F$_5$)$_3$

Recently, the sterics importance was studied by comparing TMPBH$_2$ and PipBH$_2$, and the result shows PipBH$_2$ is more active in the borylation procedure of heteroarenes than

the bulkier $TMPBH_2$. It was found that C-H activation step was easier with smaller amines. In their research[46], Fontaine et al reported that by examination of all catalysts, the most active one was the piperidine analogue (Scheme 28).

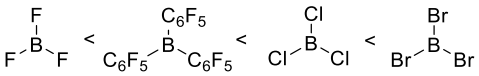


$TMPBH_2$ **64** $PipBH_2$ **65**

Scheme 28 steric study

Lewis acidic boron reagents

In FLPs, the Lewis acidity of LA and Lewis basicity of the LB defines the reactivity of the FLP. $B(C_6F_5)_3$ is a typical and strong Lewis acid, it has three perfluorinated aryl rings which present strong electron withdrawing effects. Due to its steric bulk and electron-withdrawing nature, it is a common Lewis acid in FLP chemistry. Acidity of different Lewis borons are compared (Scheme 29). Major reports about borylation contains TM catalysts which have the drawbacks of high costs, environment unfriendly and purification issues. For example, John F. Hartwig[47] reported in 2011 using rhodium and ruthenium complexes to do selectively borylation. Therefore, borocations attracted scientists attention. Boron can easily become cationic in the center, hence borocationic compounds have higher Lewis acidity.

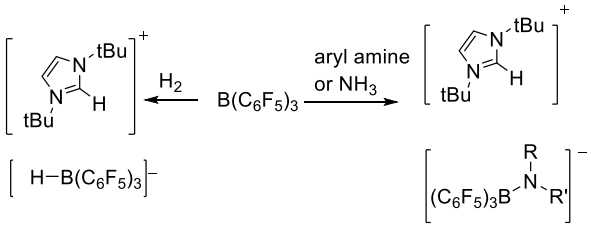


Scheme 29 Lewis acidity of boranes[48]

$B(C_6F_5)_3$

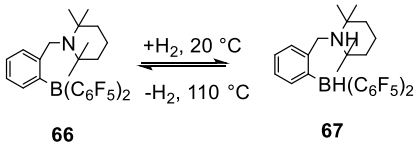
$B(C_6F_5)_3$ is known as a strong Lewis acid, it can react with nitrogen-containing Lewis bases to produce B-N coordination adduct. When compare it to other Lewis acids including $SnCl_4$, $AlCl_3$ or BF_3, $B(C_6F_5)_3$ is proven to be quite stable. The enhanced orbital interaction provide additional stabilization[49]. In 2005[50], Francesca Focante did a research about $B(C_6F_5)_3$ with nitrogen-containing compounds. $B(C_6F_5)_3$ is expected to produce adducts with the Lewis basic amines of the type R_3N (with R= aryl, alkyl, or H). In 2008[51], Chase and co-workers discovered that hydrogen and amine can be activated by a frustrated Lewis pair. In the article, the FLP derived from $B(C_6F_5)_3$ and

the sterically restricted N-heterocyclic carbene *N,N'*-*t*$Bu_2C_3H_2N_2$ can have heterolytic cleavage of dihydrogen to form a imidazolium borate and also cleave amine N-H bonds to produce aminoboranes or aminoborate salts (Scheme 30).



Scheme 30 FLPs cleaves dihydrogen and amine N-H bonds

The group of Rieger[52] reported the first *ansa*-aminoborane that is capable of co-operative hydrogenation in a reversible manner (Scheme 31).



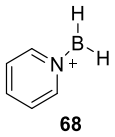
Scheme 31 Reversible H_2 activation by an *ansa*-aminoborane.

BH_2^+ cation

For intramolecular arene borylation, BH_2^+ cation can be stabilized by R_3N coordination.

In 2007, Vedejs et al.[53] reported that when using trityl cation to abstract hydride from Lewis base borane complexes ($L{\cdot}BH_3$), the borenium ions do not accumulate in this procedure. The cations bridged by the hydride have sufficient stability that the excess trityl cation can not abstract the remaining hydride.

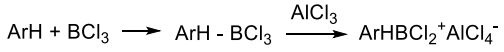
In Ryschkewitsch's report[54], the (pyridine)borenium ion was proposed as an intermediate for its characteristic three-coordinate boron cation structure(Scheme 32).



Scheme 32 the (pyridine) borenium ion

$AlCl_3$ as Lewis acid

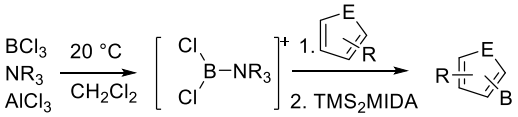
In 1960, Muetterties[55] first reported the organoborane synthesis with $AlCl_3$.



Scheme 33 organoborane synthesis with $AlCl_3$

In the reaction mechanism, the first step would be an interaction similar to the known $AlCl_3$-HCl-ArH system (Scheme 33), following by the simple loss of a proton from $ArHBCl_2^+$ by reacting with aluminum.

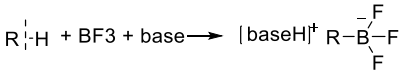
In 2013, Bagutski and co-workers[56] reported a mechanistic study into Amine-Mediated Electrophilic Arene Borylation. The research shows that the borylation does not happen for poorly activated arenes even under elevated temperature. In contrast, the product formed during the interaction of $AlCl_3$ with Y_2BCl (Y_2=Cl_2 or *o*-catecholato) (Scheme 34) is seen as a key electrophile. And it also shows that when using an extremely bulky amine, borylation reactions go through a boron electrophile produced by coordination of $AlCl_3$ and Y_2BCl or through the formation of $AlCl_3$ adduct by deprotonation and transmetalation instead of borenium cation. They demonstrated that borylation reaction mediated by amine electrophilic can produce $ArB(OR)_2$ in high yields. And different substrate scope for borylating electrophilic arene was carried.



Scheme 34 key electrophile presented

BF_3

In 2016, Iashin and co-workers[57] reported a highly reactive frustrated Lewis pair by simple aliphatic amine and BF_3 (Scheme 35). This FLPs can have C_{sp}-H borylation with terminal acetylenes. They illustrated that FLPs which are based on PMP and boron trifluoride complexes are promising reagents for activating other substrates.



Scheme 35 formation of FLPs

Summary

In conclusion, in recent studies for the preparation of organoboron reagents, Frustrated Lewis Pair (FLP) -catalyzed reactions have proven to be effective and have deserved their place alongside previous metal catalysts. These methods, they both possess their own great advantages. Transition metals have the ability to easily meditate two-electron transfer and they can conduct borylation in catalytic amount. But compared to the use of FLPs, the shortcomings of metal catalysts stand out clearly, as they often contain toxic, rare and expensive transition metals and therefore possess potential health risks and are environmentally unfriendly.

Stephan and his coworkers reported first articles about hydrogen cleavage by FLPs which actually initiated the FLPs chemistry. In a reaction characteristic of FLPs, hydrogen and later other small molecules are activated to form a specific [Lewis acid] substrate- [Lewis base] + adduct. The reactivity of FLPs can always be modified by change the acidity and basicity. For example, $B(C_6F_5)_3$ is a typically used and stronger Lewis acid compared to BF_3. Recently, it has been shown that FLPs can heterolytically split and thus activate even low reactive C-H bonds.

While exploring FLPs in C-H borylation, intramolecular 2-AABs were reported by our group to be useful in borylation of heteroarenes. 2-AABs contain boron as Lewis acidic center and nitrogen group as Lewis basic center. In this procedure, proton is abstracted by Lewis basic amino group and electron density of the C_{sp2}-H bond then transferred to acidic boron center. The highly Lewis acidic borenium cation is a central component in the borylation process. In 2-AABs BH^{2+} -cation is stabilized by R_3N coordination for arene borylation, and the generated three-coordinate boron cation is a promising intermediate for the borylation process. As a result, FLPs have a significant ability to activate C-H bonds and they are promising candidate even for catalytic C-H borylation reactions.

Experimental part

General information

Solvents were all dried in conventional methods and stored with molecular sieves. Deuterated solvents were purchased from Eurisotop or Sigma-Aldrich and dried with molecular sieves. All experiments were operated under argon atmosphere using a conventional Schlenk technique or in a glove box (Mbraun Unilab). Reagents were purchased from Sigma-Aldrich.

NMR spectra were recorded at Varian Mercury 300 (^{1}H, ^{11}B) spectrometers at 27 ˚C. ^{11}B spectra were baseline corrected. ^{11}B spectra were referenced to the shifts of external standards (BF_3•Et_2O). Chemical shifts for the ^{1}H spectra were referenced to the deuterated solvent:

- C_6D_6: $\delta = 7.16$;
- $CDCl_3$: $\delta = 7.26$;
- CD_2Cl_2: $\delta = 5.32$;

Introduction

As it was highlighted in the literature review section, the family of 2-AABs (with N and B reactive centers fixed in a chelating manner) can easily go through insertion into C_{sp2}–H bonds of simple alkenes and arenes (Fig 2, A)[29]. A specific geometrical prearrangement of LA and LB sites is crucial, as it lowers the kinetic barrier of C-H bond splitting. Previous studies has showed that *ansa*-aminopyridine supported borenium species (Fig 2, B)[29] which are isolabile to 2-AABs, possess comparable reactivity towards C_{sp2}-H-bond, which could be implemented into catalytic cycle (Fig 2, C, D).

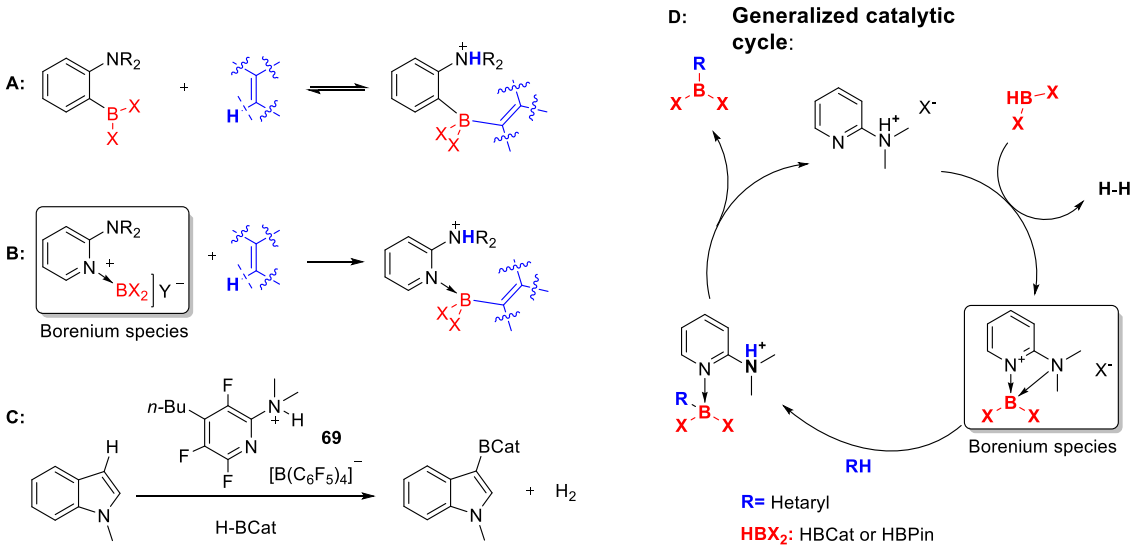


Figure 2. A:common reactivity of 2-aminophenylboranes: facile metal-free C_{sp2}–H insertion into arenes and alkenes forming zwitterions. B: General structure of 2-aminophenylboranes and their isoelectronic and isostructural cationic analogues. C: C-H Borylation of N-methylindole with H-BCat Catalyzed by **69**. D: The Proposed Mechanism of C.

As it was highlighted in the literature review part, borenium cations themselves with or even without presence of a Lewis base are capable of borylation of C-H bonds. However, typically such protocols require highly reactive boron precursors, such as BCl_3, BBr_3 and BF_3, or generation of highly reactive "naked" borenium species, which often results in poor functional group tolerance and selectivity. From another side, when coupling borenium species with FLP approach, their reactivity is defined by cumulative strength of LA and LB. This means, that less acidic borenium site can be employed and the net reactivity can be balanced by contribution of LB site (ligand assistance). Thus, borylation precatalyst **69** (Figure 2, C) would form actual reactive borenium species **70** (Figure 3, A) during catalytic cycle (Figure 3, D)**.** Despite of electron back donation from oxygenated substituents which substantially diminish Lewis acidity of **70**, it is still viable borylation agent, albeit with substrate scope limited to electron rich heteroaromatic substrates. Taking this catalytic system as a starting point for further investigation we were aiming to extend substrate scope to arenes and alkenes by increasing Lewis acidity of borenium site. Such species would be generated according to the scheme represented on the Figure 3, C from complexes between ligands with commercially available boranes by abstracting of substituent X by LA.

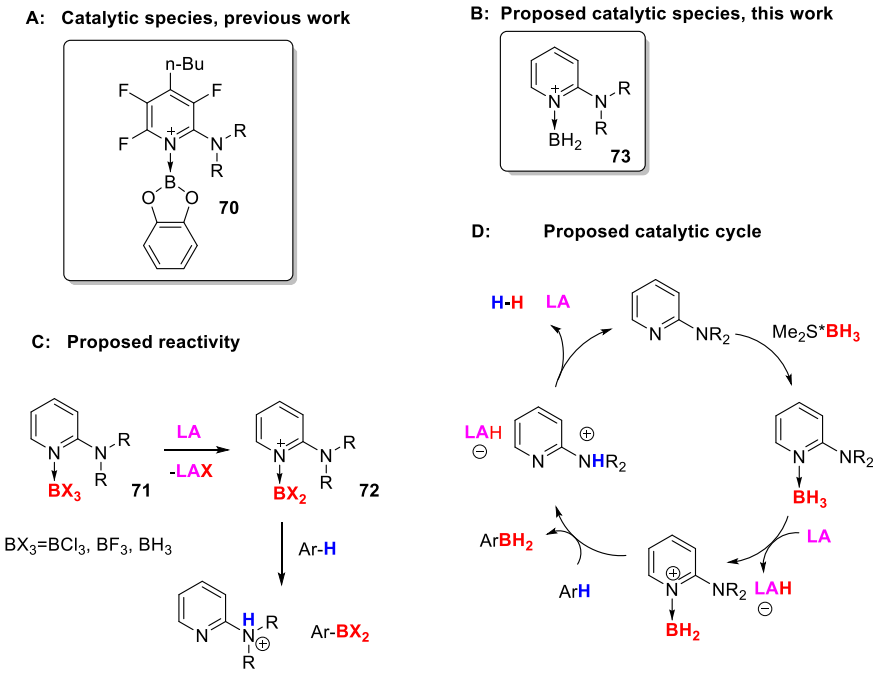


Figure 3. A: the catalytic species produced during the reaction in Fig.2 C. B: Proposed catalytic species in this work. C: Proposed reactivity in this work. D: Proposed catalytic borylation cycle

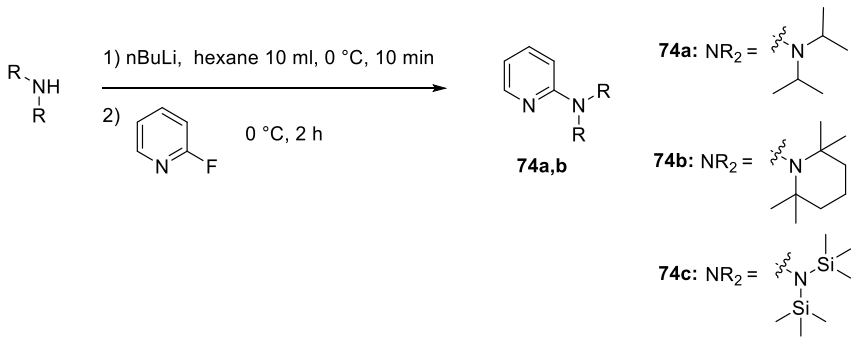
As boron precursor we proposed commercially available BH_3*Me_2S. Free BH_3 has strong hydride affinity, similar to this of BF_3, while B-H bond is relatively weak and therefore borenium species **73** can be easily generated. We envisioned, that such 2-aminopyridinyl-borenium species will be highly active and would be further incorporated into a catalytic borylation cycle D (Figure 3). After the borylation step the product $ArBH_2$ would be converted to pinacol boronate ester which is air-stable and can be readily used in cross-coupling reaction. The method proposed in the present work implies cooperative actions of LA, which serves as a reagent itself, and LB, which can be fully recovered from the reaction mixture. Thus, this approach offers high atom efficiency and low waste generation. The proposed catalytic systems feature high substituent variability and can be, hence, tunable to achieving efficient catalytic parameters. One can vary the substituents R and R' at the nitrogen, at the aromatic core, a source of boron and the nature of a weakly coordinated counter-anion. Moreover, rational ligand design would provide an additional tool for finetuning selectivity.

Results and discussion

Synthesis of ligands and borane complexes.

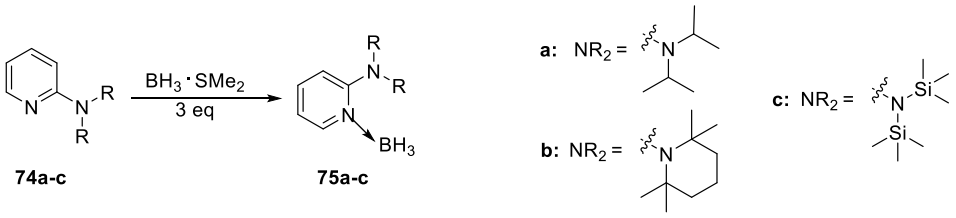
We first synthesized two ligands **74a,b**; ligand **74c** has been synthesized previously in

our laboratory. These ligands are derivatives of *ansa*-aminopyridine, and feature bulky substituents at nitrogen. Thus, nitrogen site will act as proton acceptor, but is prevented from strong coordination with highly Lewis acidic boron unit, which would quench reactivity of corresponding borenium species.



Scheme 36 Synthesis of *ansa*-aminopyridine ligands.

Further, **74a-c** were transformed to borane complexes **75a-c** simply by mixing ligand with excess of $BH_3{\cdot}SMe_2$ under inert atmosphere overnight. *Ansa*-aminopyridines **74a-c**, being stronger donors replace SMe_2 in the complex. Target borane complexes could be purified by removing free SMe_2 and excess of $BH_3{\cdot}SMe_2$ on vacuum of oil pump to afford pure **75a** (60% yield), **75b** (76% yield) and **75c** (95% yield), and were characterized by ^1H and ^{11}B NMR. In all cases, ^{11}B NMRs featured a single quartet around -15 ppm corresponding to boron of **B**H_3, and ^1H NMRs featured characteristic broad quartet corresponding protons of B**H**$_3$ at 2-3 ppm in addition to set of signals belonging to the ligand.

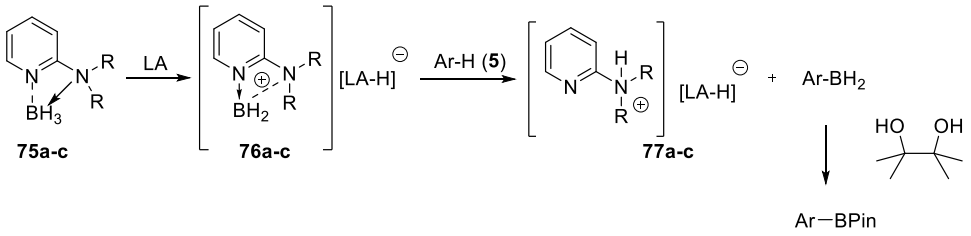


Scheme 37 Synthesis of *ansa*-aminopyridine borane complexes.

Generation of borenium cations

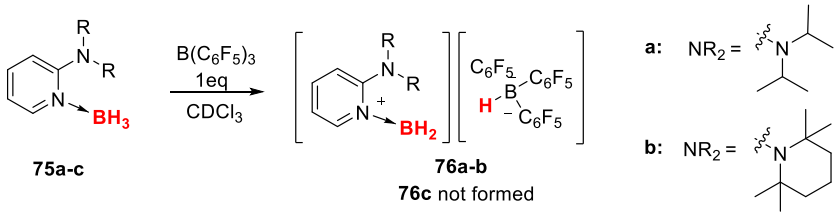
In the next step we were aiming to generate borenium species by abstracting one hydride from the complexes **75a-c** by a Lewis acid to form ligand supported borenium cation $[L\text{-}BH_2]^+$ with weakly coordinated anion $[LA\text{-}H]^-$ as indicated on the **Scheme 38**. We hypothesized that this species would further react with ArH via sp^2CH insertion

initiated by cooperative action of Lewis acidic boron center and basic of ansa-aminopyridin borenium species, and the product of borylation will further dissociate from the protonated ligand. This is due to the reduced electrophilicity of boron on substitution for H instead of pinacol which donates more electrons. The obtained borylation product $ArBH_2$ could be further transformed subsequent one-pot transesterification. The larger and stronger electron-donating diol, pinacol forms similar pinacol boronate esters that are more resistant to protodeboronation[58] in the presence of H_2O and are versatile reagents for cross-coupling reactions.



Scheme 38 General scheme for generation of *ansa*-aminopyridine suppoted borenium species and its hypothesized reactivity towards arenes ArH.

To probe this hypothesized reactivity pattern we chose to use BCF for hydride abstraction step as it possess high hydricity (affinity to hydride ion)[59]. In the glovebox in three separate vials we mixed complexes **75a-c** with equimolar amount of BCF in $CDCl_3$, and after 30 minutes measured ^1H and ^{11}B NMR spectra of obtained crude mixtures. We were delighted to find that in the reactions with **75a,b** the expected borenium species indeed were formed, as was confirmed by ^1H and ^{11}B NMR spectroscopy. To illustrate, ^{11}B NMR spectra represented on the Figure 4 features two peaks: broad triplet corresponding to **B**H_2 at about 3 ppm and sharp doublet corresponding to **B**H at about -25 ppm. Similar spectra is observed for **76b** (Figure 5). Thus, the shape and the chemical shifts of boron signals are consistent with the expected structure of the product. In case of **75c** unidentified mixture was obtained, which is presumably due to intolerance of N-Si bonds to highly acidic borane.



Scheme 39 Reaction of *ansa*-aminopyridine borane complexes with BCF.

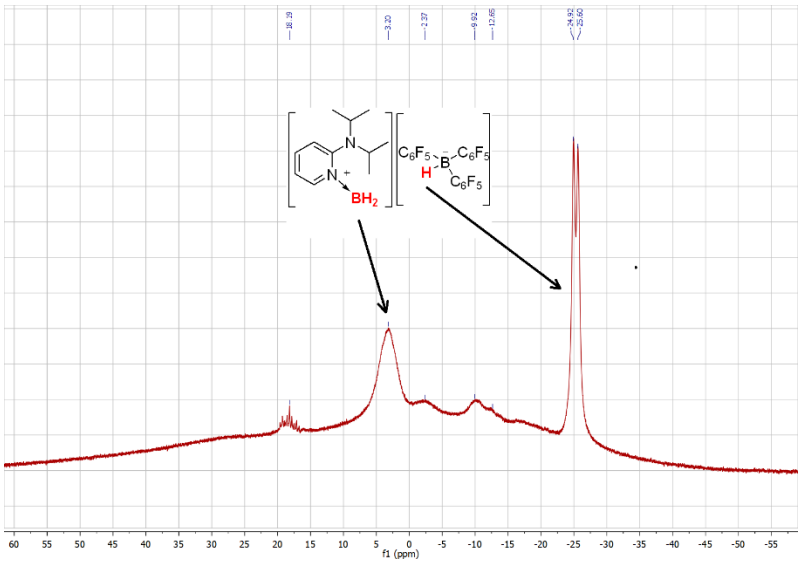


Figure 4 ^{11}B NMR spectrum of **76a**

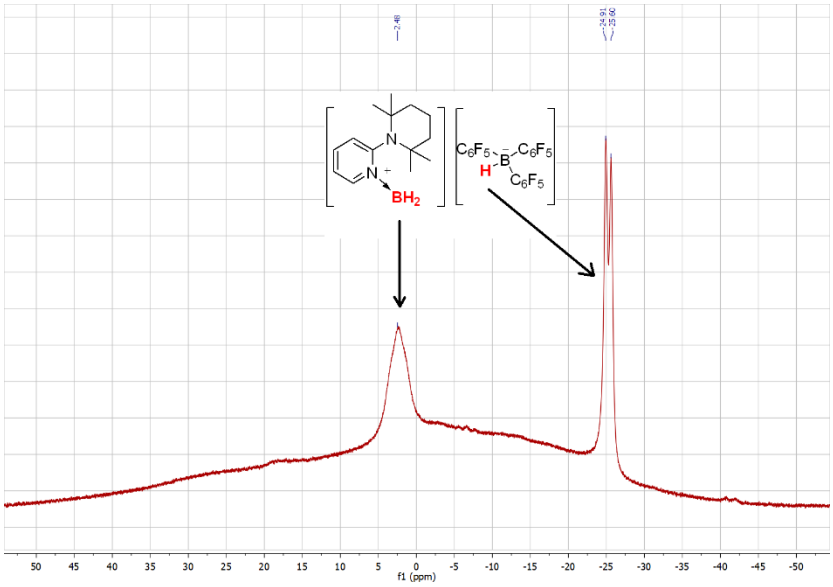
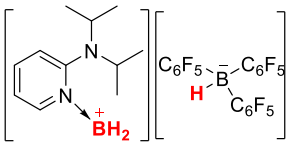


Figure 5 ^{11}B NMR spectrum of **76b**

We noted, that both spectra featured other minor peaks (in case of **76a** more visible than for **76b**). We assumed that it might be due to the tendency of boranes BAr_3 to form mixed boranes $BH_n(C_6F_5)_{3-n}$ in presence of strong hydride donors (E-H bonds). Well known illustration is the synthesis of Piers borane $BH(C_6F_5)_2$ which can be accomplished by reacting $B(C_6F_5)_3$ with Et_3SiH. Moreover, while staying in the solution $BH(C_6F_5)_2$ undergoes dismutation forming mixture of $BH_2(C_6F_5)$ and $B(C_6F_5)_3$.

Therefore, we initiated studies on the stability of **76a-b** at room and elevated temperature by monitoring ^{11}B NMR spectra. The results are depicted on the Figure 6 and 7, and indicated, that both species are relatively stable at room temperature, while

decompose upon heating to form one major species. Additional peaks, appearing in ^{11}B NMR might indicate the formation of mixed borane species such as $HB(C_6F_5)_2$, $H_2B(C_6F_5)$ or their complexes with the ligand.



76a

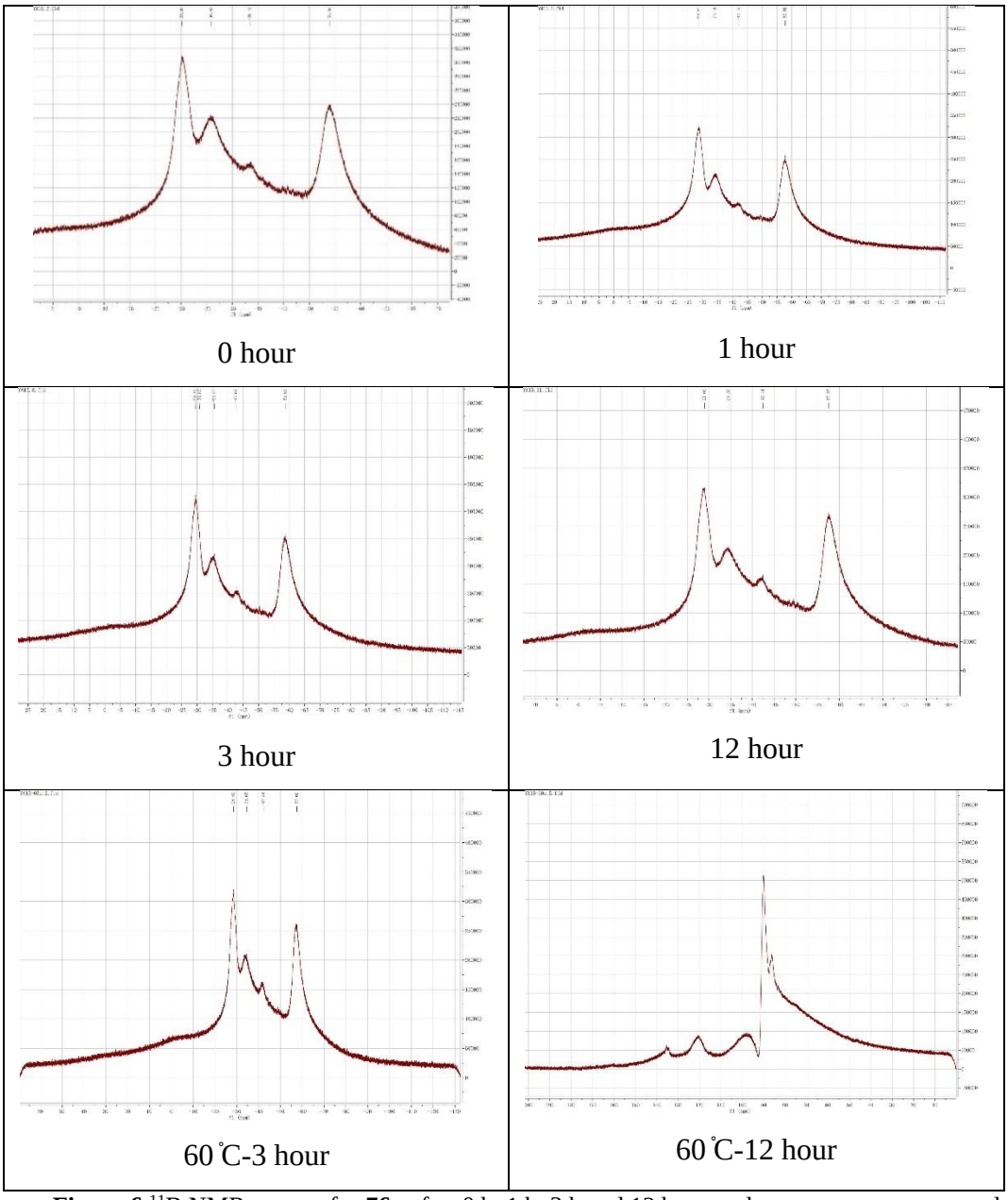
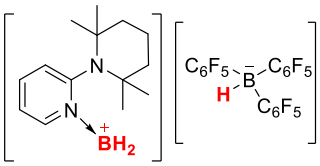


Figure 6 ^{11}B NMR spectra for **76a** after 0 h, 1 h, 3 h and 12 hour under room temperature and after 3 h, 12 h under 60℃ in $CDCl_3$.



76b

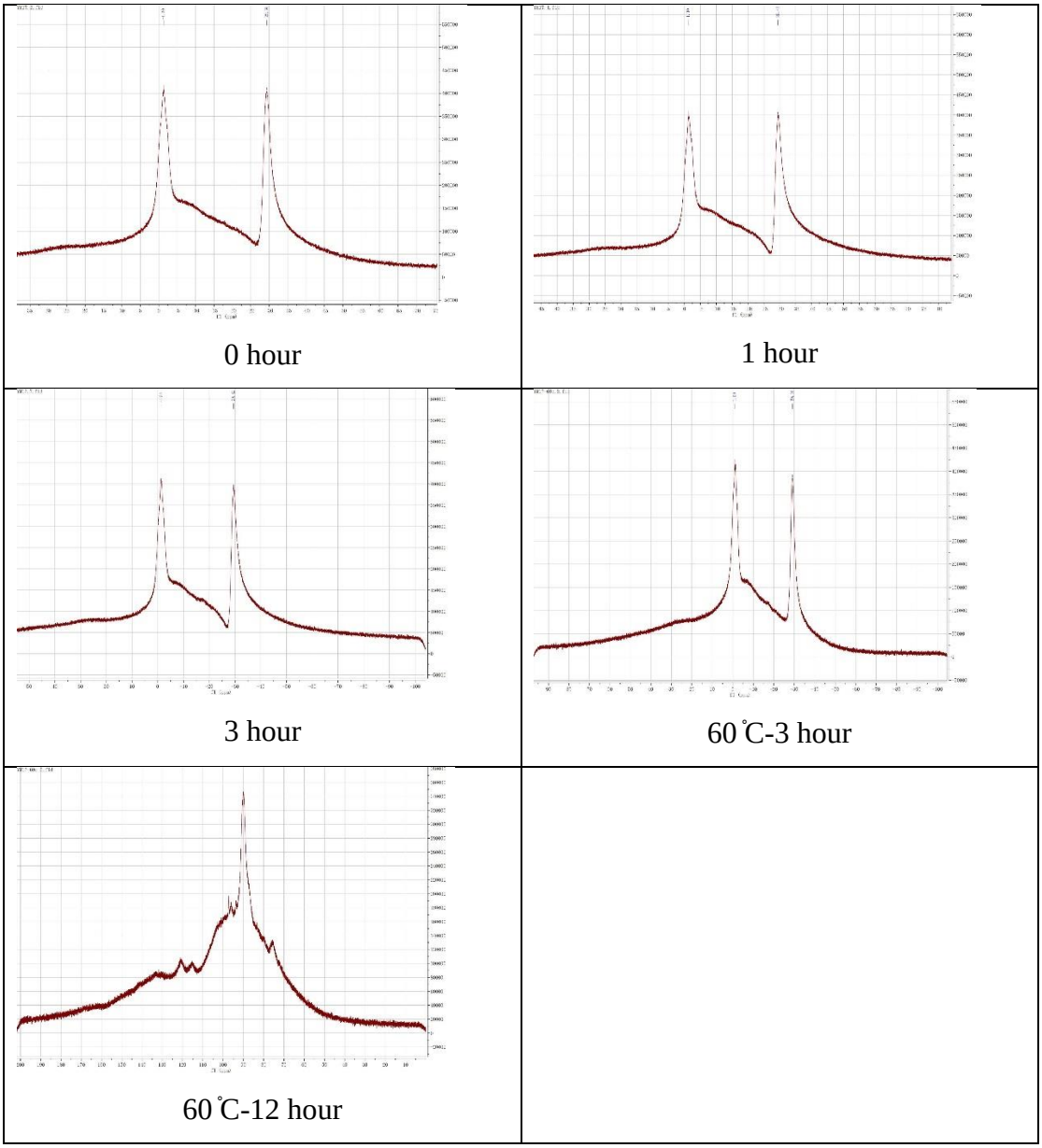


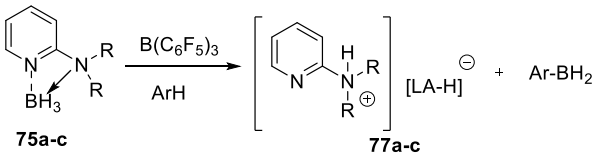
Figure 7 ^{11}B NMR spectra for **76b** after 0 h, 1 h, 3 h and 12 hour under room temperature and after 3 h, 12 h under 60℃ in $CDCl_3$.

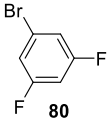
Borylation reactions

After we confirmed the formation of ligand supported borenium species **76a,b**, we set to investigate their reactivity as borylation agents. As model substrates we chose heteroaromatic 3-methylthiophene, 2-methylthiophene, and electron deficient arene as they possess relatively weak (acidic) C_{sp2}-H bonds. The borylation experiments with

75a,b were set up as following: in the glovebox **75** and $B(C_6F_5)_3$ were mixed in $CDCl_3$ in a vial and stirred vigorously for about 10 mins, then substrate (**78-80**) was added and the solution was divided between two NMR tubes. One sample was kept at room temperature and another at 60°C. The reaction mixtures were analyzed by crude ^1H and ^{11}B NMR spectra (**Table 1**). The resonance of methyl group of 3- and 2-methylthiophenes was used as anchor signal to roughly estimate reaction outcome, as it stands out from crowded areas of the spectra. For instance, **78** has its characteristic CH_3 signal at 2.30 ppm. After borylation in the crude ^1H NMR two new signals appeared next to this of **78**: smaller peak at 2.35 ppm and minor peak is 2.39 ppm. We assumed that these peaks belong to products borylated into different positions. The conversion was estimated with respect to total integral of all CH_3 signals. Similarly, 2-methyl thiophene **79** has its characteristic CH_3 signal at 2.51 ppm. After borylation in the crude ^1H NMR additional peak at 2.64 ppm appeared. Upon heating better conversion could be obtained. This indicates, that heating might be crucial for the reaction to proceed and the borylation system stable under heating is highly desirable.

Table 1 **75a** and **75b** was tried with three different substrates in $CDCl_3$, NMR crude conversion.



Catalyst	 **78**	 **79**	 **80**
75a	17% at 25 ˚C and 60 ˚C.	35% at 25 ˚C and 60 ˚C.	No product
75b	Trace	Trace at 25 ˚C and 46% at 60 ˚C.	No product

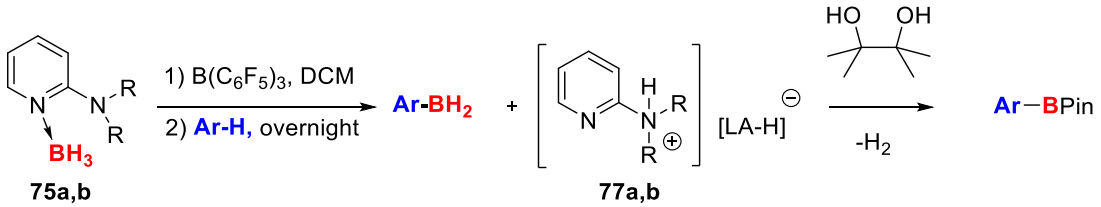
When **75b** was tried with **78**, the spectrum shows no product peak. Absence of reactivity compared to **75a** presumably is due to steric factor (bulky TMP group). The spectrum shows no change after heating. When **75b** was tried with **79,** the spectrum of this reaction shows one major peak is 2.51 pm from the 2-methyl thiophene, and two tiny peaks. The conversion of the reaction is very small compared this with **75a**. The reason

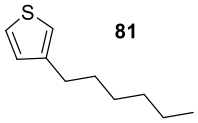
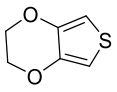
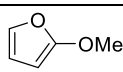
may be that TMP is large and occupy large space than ipr_2. When heated at 60 ℃, result shows better conversion, 2.51 ppm is from the staring 2-thiophene. There are two more peaks 2.61 ppm and 2.64 ppm indicating the borylation happens in two different positions. And heating can help thiophene to be borylated. No product formation was observed with **80**. This indicates, that cumulative strength of LA and LB parts of ligand supported borenium species is not enough to break strong C_{sp2}-H bonds of arenes.

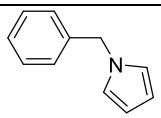
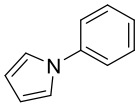
Exploring substrate scope

We further investigated the substrate scope: various heteroaromatic substrates, including thiophenes, furans and pyrroles. As borylated product $ArBH_2$ is air and moisture sensitive, the reactions were quenched by pinacol to isolate product in form of pinacolate esters of corresponding boronic acids. By analyzing the spectrums and adding internal standard, the conversion could be calculated. In the reactions with different substrates, due to the small amount mesitylene was added as internal standard to calculate NMR yields.

Table 2 results of reactions with different substrates. Yield is calculated from NMR.



Ar-H	**75a**	**75b**
 **78**	40%	n.d., MS detected
 **79**	51%	n.d., MS detected
 **80**	56%	28%
 **81**	n.d., MS detected	n.d., MS detected
 **82**	n.d., MS detected	n.d., MS detected
 **83**	n.d., MS detected	n.d., MS detected

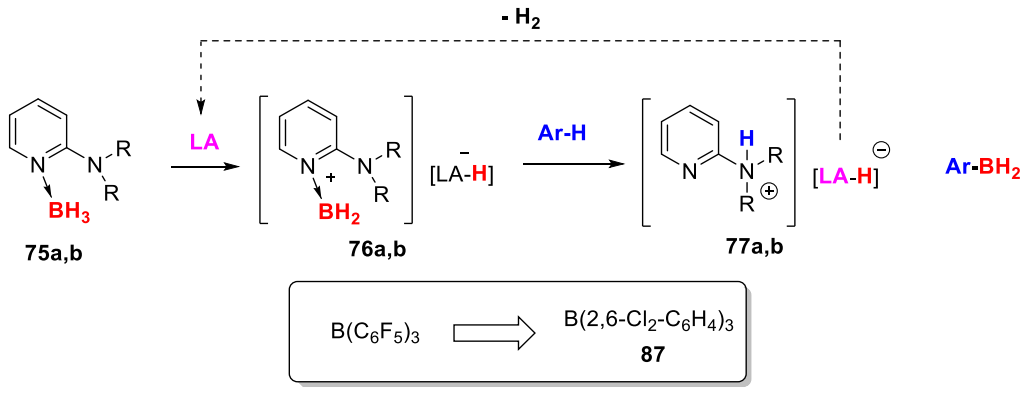
 84	n.d., MS detected	n.d., MS detected
 85	No product	19%
 86	No product	15%

The reactions solution was analyzed by TLC. The mark with product mass means the TLC result gives points containing the product mass.

The isolation is done by flash silica chromatography, the low isolated yield may be caused by protodeborylation induced by silica. In some cases the product could not be isolated but was detected on TLC plate by express TLC/MS.

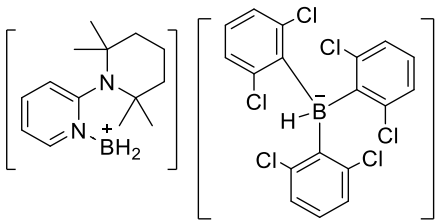
Other Lewis acids for hydride abstraction.

Thus, in our proof-of-principle experiments we showed that the borenium species generated from *ansa*-aminopyridine borane complexes act as borylation agent. Next we were aiming to implement this reactivity in catalytic cycle as represented on Figure 3, D. In our borylation protocol we use stoichiometric amounts of expensive $B(C_6F_5)_3$, which is not atom efficient and practical. Moreover, since CH bond might require it was showed that it not stable under heating, which is BCF has strong hydride affinity and because of this it is one of the most commonly used LA counterpart in FLP chemistry. In this sense **77a,b** can be considered as classical FLP – H_2 adduct. It is known, however, that hydrogen activation by FLP can be reversible and we anticipated, that if we use borane with lower hydride affinity than that of $B(C_6F_5)_3$, the obtained ionic pair will release hydrogen. In this case LA will be regenerated and the reaction would work in catalytic fashion.



Scheme 40 tris(2,6-dichlorophenyl)borane for hydride abstraction.

We first probed commercially available BPh_3 as LA to abstract hydride from complexes **75a,b**. ^{11}B NMR spectrum of the reaction mixture shows appearance of many peaks, indicating that BPh_3 undergoes rapid dismutation, which presumably due to reduced sterics, compared to $B(C_6F_5)_3$. Also, no borenium species is formed meaning, that hydride affinity of BPh_3 is too low. Therefore, we synthesized more Lewis acidic and sterically hindered borane tris(2,6-dichlorophenyl)borane **87**(Scheme 40). When **87** was mixed with **75a** or **75b**, crude ^{11}B NMR confirmed the formation borenium species **88a,b** .



88a

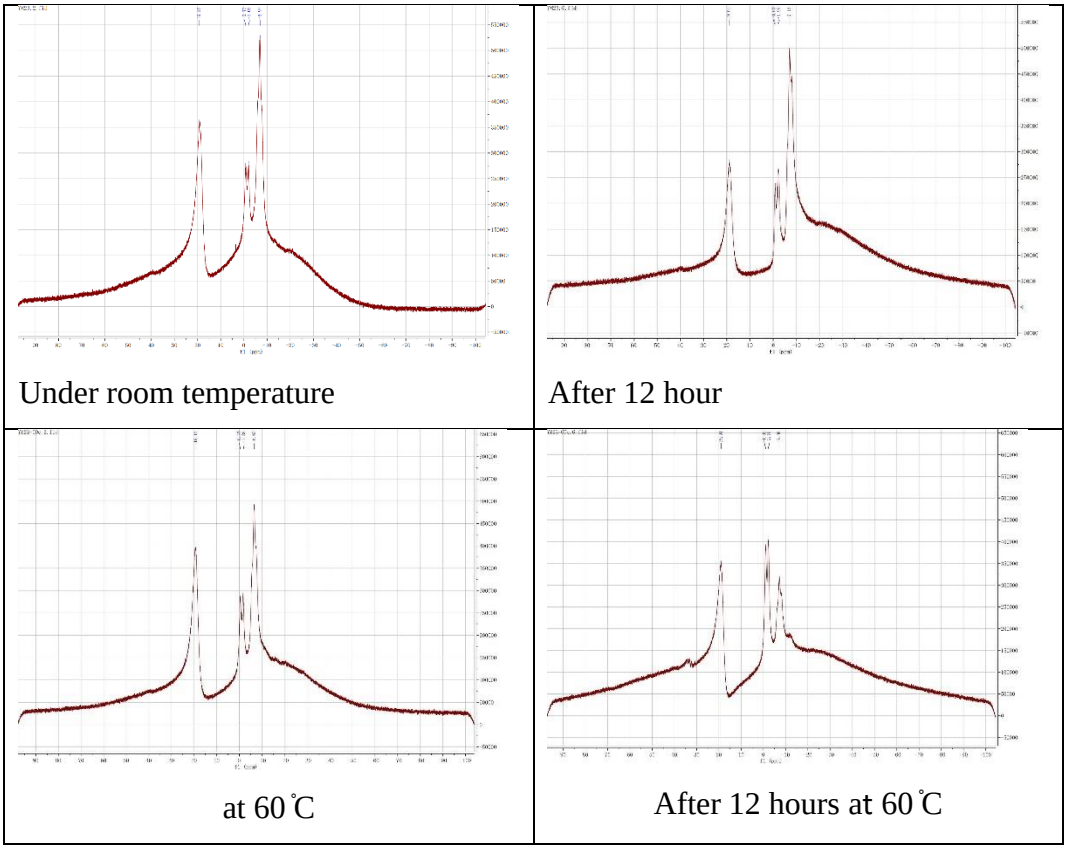
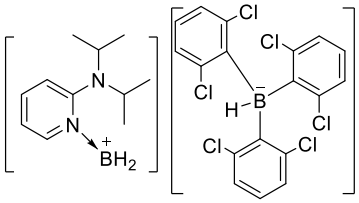


Figure 8 ^{11}B NMR spectra for **88a** after 0 h and 12 hour at room temperature and after 12 h under heating

Under room temperature, the boron spectrum features three peaks, the double peak is presumably from the $HB(PhCl_2)_3^-$ and the triple peak is from L-TMP-BH_2^+. After heating at 60 ℃, the boron spectrum almost same indicating the FLPs is quite stable.



88b

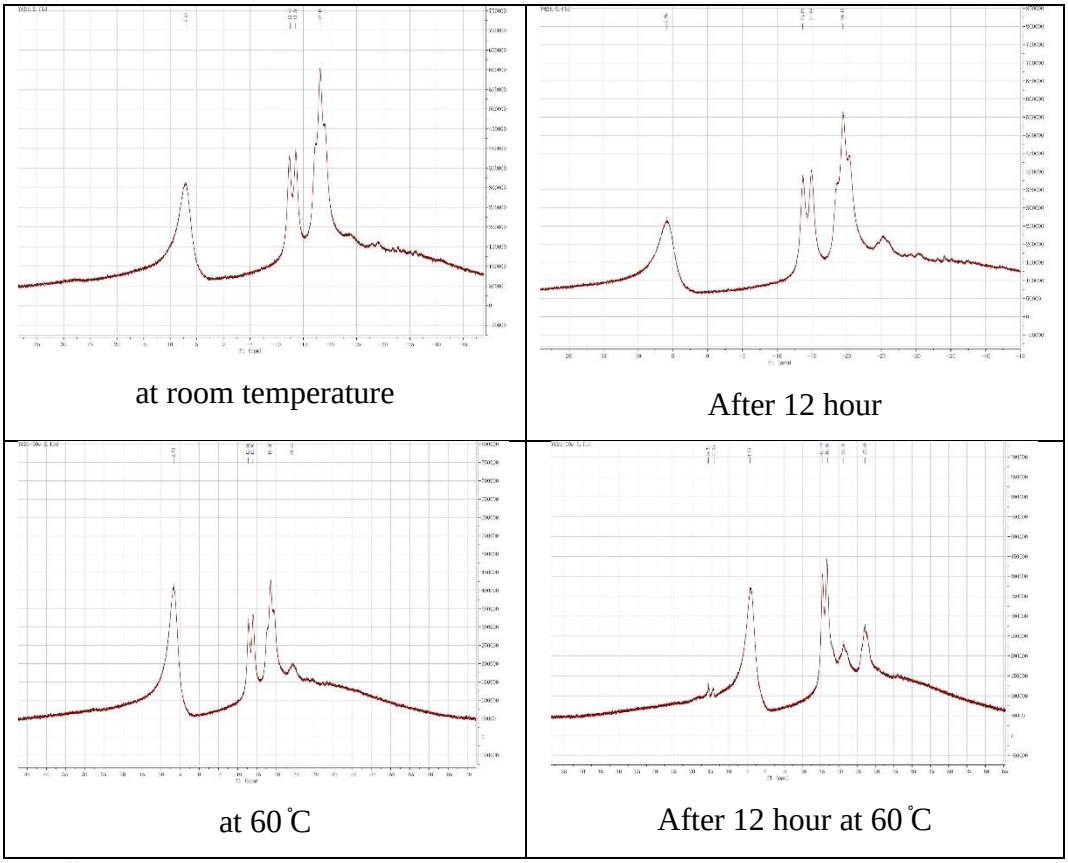
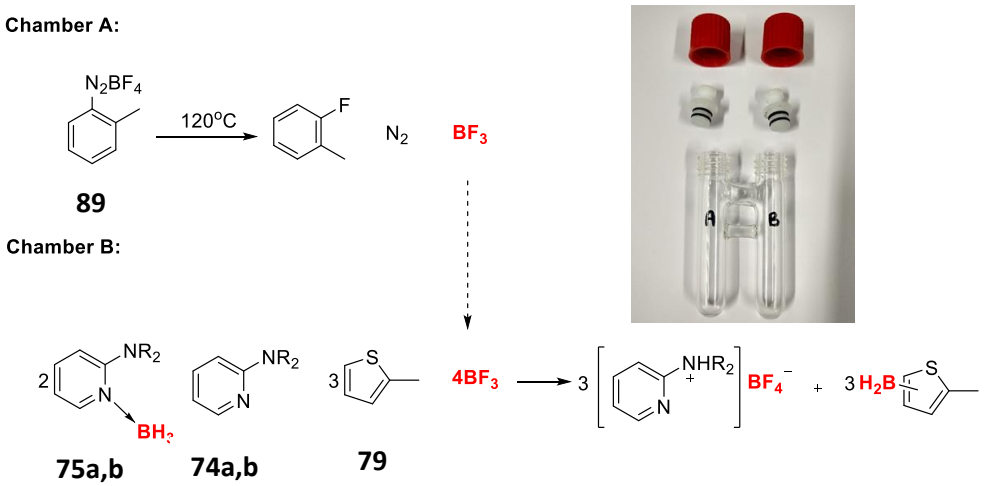


Figure 9 ^{11}B NMR spectra for **88b** after 0 h and 12 h at room temperature and after 12 h under heating

Under room temperature, the boron spectrum have three peaks, the double peak is from the $HB(PhCl_2)_3^-$ and the triple peak is from 3-BH_2^+. After heating at 60 ℃, the boron spectrum almost same indicating the FLPs is quite stable. But after heating for longer time, the FLPs is becoming unstable and other peaks show up. ^{11}B spectrum indicates one triple peak disappear and a new triple peak show up. And the double peak for $HB(PhCl_2)_3^-$. However, when this species **88a,b** were probed in borylation of 1-methyl-pyrrole no product was observed.

Replacing BCF with BF_3.

As we could not achieve borylation process in catalytic manner, we considered that expensive $B(C_6F_5)_3$ could be replaced by cheap BF_3 which has similar, albeit slightly lower, Lewis acidity. To avoid working with highly toxic and corrosive gaseous BF_3, we established a very practical method for generating BF_3 in situ from solid precursor in two-chamber glass reactor. As solid precursor of BF_3 we used benzene diazonium tetrafluoroborate **89**. In a typical procedure **89** was placed in the chamber A and borylation would occur in the chamber B. BF_3 released by heating in the chamber A, and then is diffused in the reaction mixture solution (in DCM) in the chamber B.



Scheme 41 two chamber reactions with BF_3

Table 3 trial with BF_3 using two chamber reactors

	Chamber A:	**Chamber B:**	Results
Trial 1	4 eq of **89** Heat slow at 120 ̊C	3 eq **79**, **74a**, **75a**	Trace conversion
Trial 2	4 eq of **89** Heat immediately at 120 ̊C	3 eq **79**, **74a**, **75a**	Trace conversion
Trial 3	8 eq of **89** at 120 ̊C Heat immediately	3 eq **79**, **74a**, **75a**	Product: Starting = 0.44: 1
Trial 4	8 eq of **89** at 120 ̊C Heat immediately	3 eq **79**, **74b**, **75b**	Product: Starting = 1.44: 1
Trial 5	8 eq of **89** at 120 ̊C Heat immediately	3 eq **79**, **74b**, **75b**	Product: Starting = 0.87: 1
Trial 6	4 eq of **89** at 120 ̊C	3 eq **79**, **74b**, **75b**	No product

	Heat immediately		
Trial 7	8 eq of **89** at 120 ℃ Heat immediately	3 eq **78**, **74b**, **75b**	Product: Starting = 0.3: 1
Trial 8	8 eq of **89** at 80 ℃ slowly	3 eq **79**, **74b**, **75b**	Product: Starting = 0.44: 1
Trial 9	8 eq of **89** at 80 ℃ slowly	3 eq **78**, **74b**, **75b**	Product: Starting = 0.72: 1
Trial 10	8 eq of **89** at 80 ℃ slowly	3 eq **79**, **74a**, **75a**	Product: Starting = 0.13: 0.38
Trial 11	8 eq of **89** at 80 ℃ slowly	3 eq **78**, **74a**, **75a**	Product: Starting = 0.98: 1
Trial 12	6 eq of **89** at 80 ℃ slowly	3 eq **79**, **74b**, **75b**	No product
Trial 13	10 eq of **89** at 80 ℃ slowly	3 eq **79**, **74b**, **75b**	Product: Starting = 1.4: 1
Trial 14-repeat of 13	10 eq of **89** at 80 ℃ slowly	3 eq **79**, **74b**, **75b**	Product: Starting = 0.98: 1
Trial 15	16 eq of **89** at 80 ℃ slowly	3 eq **79**, **74b**, **75b**	Product: Starting = 0.78: 2.87
Trial 16	8 eq of **89** at 80 ℃ slowly	3 eq **79**, **74a**, **75a**	Product: Starting = 0.44: 0.8
Trial 17	8 eq of **89** at 80 ℃ slowly	3 eq **78**, **74a**, **75a**	Product: Starting = 0.45: 1

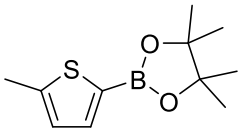
After analyzing and comparing the ^{1}H NMR spectrum, the reaction with **74a** and **75a** system has the best conversion. But there are three products, the selectivity is not good. The reason might be that BF_3 is very small compared to BCF.

75b is also tried with **79** in DCM, the conversion is better, after adding pinacol, the conversion is calculated as 1.4: 1 (product : starting material)

Because of the previous diazonium salt is not stable, new diazonium salt is synthesized with 95.8% yield as light yellow brown powder stored in freezer and wrap with aluminum foil.

The reaction is followed by adding pinacol, then dried under vacuum.

When conducting the analysis, **trial 16**, **17** show product mass **79a** in GC which is 224 (m/z).



79a

Scheme **42** one possible borylation product of **79**

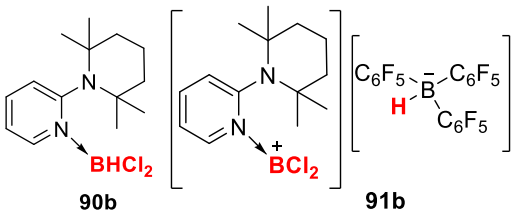
Discussion

There is a interesting phenomenon when trying BF_3, the TMP part can be seen in the NMR spectrum. Here is an assumption that, Boron reacts with TMP and then transfer it to the thiophene.

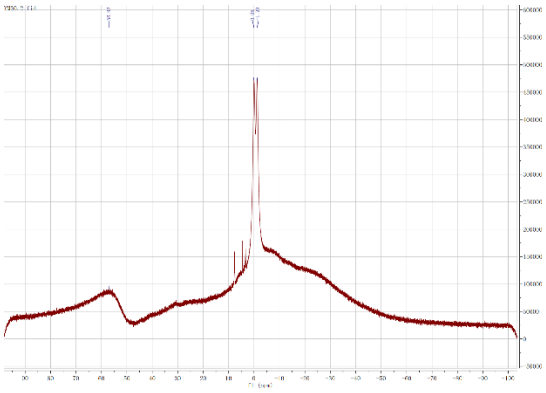
In the later part of the research, **74a** is more often used than **74b** trying with different substrates cause FLPs with smaller amines generate more active catalysts for the metal-free borylation of heteroarenes, surpassing the activity with bulkier TMP derivatives[46]. However, this is just the scratch of the boron catalyst in C_{sp2}-H borylation. How to push reaction forward, to improve the product selectivity and the way of energy change in the supposed mechanism is still need further research.

Exploration of other boron sources

Another weak point of our protocol is limited substrate scope and low conversions. We assumed the BH_2^+ group may not be electrophilic enough to attack a thiophene ring, which gives the thinking that make boron centre more electrophilic. The thought was to add Cl ligands into boron centre. The -Cl group will attract electron and make boron centre more electrophilic. **90b** was prepared by putting **74b** and $BHCl_2(CH_3)S$ together and stir overnight. FLPs **91b** was monitored. (Scheme 43).



90b **91b**



Scheme 43 ^{11}B NMR spectrum of **91b**

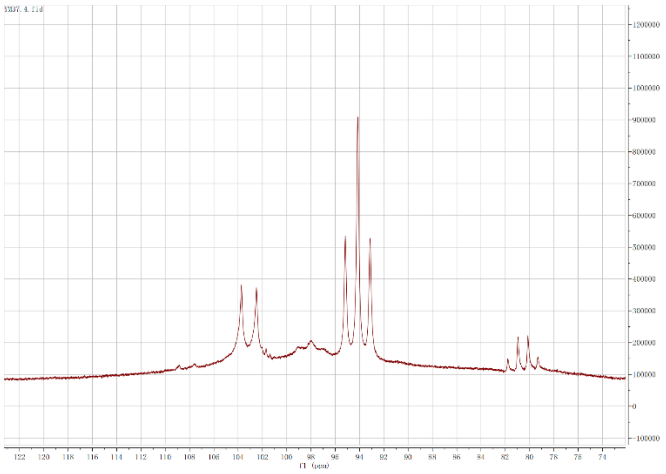
The boron spectrum of **91b** shows the characteristic peak. Single peak corresponding to L-**B**Cl_2^+ at about 56.9 ppm and double peak corresponding to H**B**CF^- at around 0 ppm. It is stable after long time at room temperature but not stable under heating. The spectrum indicates it is qualified for the next borylation of thiophene.

In the glovebox, **91b** was mixed with **79** in two vials, one with $CDCl_3$ and the other with C_6D_6.

Based on the result before, higher temperature can help thiophene to lose the proton. In this case, the reaction in $CDCl_3$ is heated at 60 ℃. The spectrums show only starting material peak which is 2.51 ppm, showing no borylation happens. Indicating that the FLPs is not strong enough. In order to eliminate the effect of solvent, C_6H_6 was selected as the solvent and the temperature was increased to 100 ℃. While the spectrum shows that only starting material and very small amount of product.

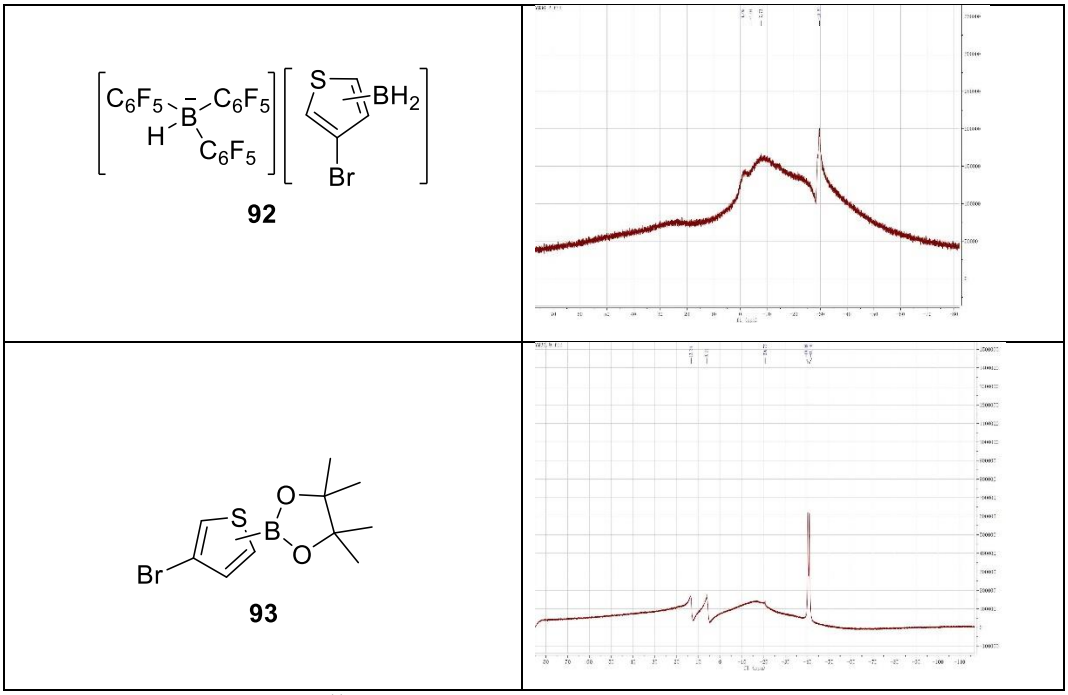
After confirming the BCl_2 have no positive effect on the borylation, **76a** and **76b** were tried with 3-Br-thiophene in $CDCl_3$. Spectrums indicate no borylation happens under room temperature. And under heating, there is only minor change. The reason may because that $HB(C_6F_5)_3$ keep exchanging and form three different products with -C_6F_5.

By realising $BHCl_2$ is not working, BH_2Cl is tried by mixing Me_2SBH_3, BCl_3 and Me_2S together. **74a** was tried with BH_2ClSMe_2 to form amino-boron complex. But the reaction keeps exchange (Scheme 44). After few attempts, we keep this thought aside and move on.



Scheme 44 ^{11}B NMR spectrum of reaction with BH_2ClSMe_2

76a was tired with 3-Br-thiophene in CH_2Cl_2. The ^1H NMR spectrum of **92** shows few more peaks and boron spectrum shows different as well. In order to further confirm there are products, pinacol is added to form **93**. Boron spectrum indicates there are two peaks around 30 ppm corresponding to the **B**pin.



Scheme 45 ^{11}B NMR spectra before and after pinacol in DCM

$AlCl_3$

It is noteworthy that $AlCl_3$ can enable arene borylation with BCl_3 to yield aryldihaloboranes. In this process, $[BCl_2]^+[AlCl_4]^-$ is formed.**74** were transformed to boron complex simply by mixing ligand with excess BCl_3 in glove box, stirring overnight and dried under vacuum to afford **74a**-BCl_3 with 93.7% yield, **74b**-BCl_3 with

64.3% yield. **78** as model substrate was tried with **74a**-BCl_3 and **74b**-BCl_3. The conversion result is indicated in Table 4.

Table 4 try 2-methylthiophene as substrates

	 **78**
74a-BCl_3, $AlCl_3$ in $CDCl_3$	Conversion: 1.17:1(product: starting material)
74b-BCl_3, $AlCl_3$ in $CDCl_3$	Conversion: 1:2(product: starting material)

Conclusions

In conclusion, new strategies for the metal-free C_{sp2}-H borylation was developed during my master's thesis. We showed that *ansa*-aminopyridine supported borenium species **75a,b** derived from ansa-aminopyidine borane complexes **74a,b** via hydride abstraction are viable borylation agents for heteroaromatic substrates such as thiophenes and pyrroles, giving low to moderate conversions. **75a,b** are stable under ambient conditions, but decompose upon heating. Since the method does not involve TMs and the ligand can be recovered from the reaction mixture, it is more atom efficient compared to conventional methods.

To avoid using stoichiometric amounts of Lewis acid to generate borenium species, attempted to make this process catalytic with respect to LA by employing less acidic LA tris(2,6-dichlorophenyl)borane. Although the borenium species could be generated with this borane as well, borylation did not occur. This indicates, that reactivity of the borenium species is sensitive to the nature of the weakly coordinated ion (presumably steric effect, that prevents substrate to approach borenium cation).

Since we failed to find LA which would work in catalytic amounts, we proposed to replace expensive $B(C_6F_5)_3$ with cheap BF_3. To avoid working with highly toxic and corrosive gaseous BF_3 from the gas cylinder we proposed to generate it from a solid precursor, benzenediazonium tetrafluoroborate, which release BF_3 upon decomposition when heated. We conducted the borylation reaction in the two chamber glass reactors, in which BF_3 is generated in one chamber and the reaction occurs in another.

We demonstrated that our borylation procedure is reproducible. However, further investigation is required in order to increase conversions and extend substrate scope, as well as perform process in catalytic manner.

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Appendice